Inamed Clinical Summary Memorandum

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FDA/CDRH/ODE/DGRND HFZ-410

Subject: Summary of prospective clinical data contained in PMA # P020056, McGhan Silicone Gel-Filled Breast Implants, including responses to FDA's major deficiencies submitted in Amendment 3 dated June 12, 2003 and in electronic mail, sponsored by Inamed Corporation.

To: The Panel

[redacted]

TABLE OF CONTENTS

I. BACKGROUND

A. Regulatory History

Silicone gel-filled breast implants have been on the market in the U.S. since 1963, prior to the May 28, 1976 date when the Medical Device Amendments were enacted, giving FDA the authority to regulate medical devices such as breast implants. In 1976, breast implants were originally placed into the Class II regulatory category following a FDA General and Plastic Surgery Devices Panel. In 1988, FDA issued a final rule classifying breast implants into Class III, with the requirement that a Premarket Application (PMA) submission would be needed after 30 or more months. In April of 1991 FDA required manufacturers to submit, by July of 1991, PMA's demonstrating the safety and effectiveness of silicone gel-filled breast implants. McGhan Medical Corporation (now Inamed) submitted PMA # P910044. In November of 1991, FDA convened an Advisory Panel to determine whether the data contained in the PMA's were sufficient. The Panel concluded that there was insufficient information to determine whether silicone gel-filled breast implants were safe and effective. Despite this inadequate data, the Panel voted unanimously to advise the FDA that because of a public health need, the implants should remain available on the market for breast reconstruction or revision of existing breast implants while manufacturers collect information to demonstrate the safety and effectiveness of the implants.

On January 6, 1992 FDA called for a voluntary moratorium on the use of silicone gel-filled breast implants while the Agency reviewed additional safety information submitted following the November 1991 Advisory Panel Meeting. In February of 1992, the Advisory Panel met to review this additional safety information, which focused on reports of autoimmune diseases in women with breast implants, information on excessive leakage of some implant models, as well as detection methods for "silent rupture." The Panel concluded that there was insufficient evidence to establish a cause-and-effect relationship between implants and immune-related or connective tissue disorders, but that because of a lack of information on the safety of gel-filled breast implants, new implantations should be limited to women participating in clinical studies which would be designed to collect safety information.

In April of 1992, FDA denied PMA approval for augmentation for all silicone gel-filled breast implants (including P910044), lifted the voluntary moratorium, and allowed availability of gel-filled breast implants based on 3 stages of availability: Stage 1 "Urgent Need" for those patients in the process of breast reconstruction or revision of existing implants; Stage 2 "Adjunct Clinical Studies for Reconstruction/Revision" designed to make the implants available for patients seeking breast reconstruction or revision of an existing implant and to collect short term (i.e. 3-5 years following implantation) safety information; and, Stage 3 "Core Study" clinical studies for both augmentation and reconstruction designed to collect local complications and effectiveness information.

In January of 1996, FDA sent letters to breast implant manufacturers indicating the general types of information anticipated in a Core Study protocol, including sample size estimates, separate evaluation of augmentation and reconstruction patients, a determination of silent rupture, connective tissue screening, determination of gel bleed, and quality of life assessments. FDA provided additional clarification of these items as well as specific types of data analyses and presentation in its "Guidance for Saline, Silicone Gel, and Alternative Breast Implants; Guidance

for Industry" (herein referred to the Breast Implant Guidance Document), initially issued on October 5, 1999, updated on August 13, 2001, and replaced by the current version on February 11, 2002 which is available at http://www.fda.gov/cdrh/ode/guidance/1354.pdf.

On March 30, 1998, McGhan Medical (now Inamed) received FDA approval of their Adjunct Clinical Study for patients undergoing breast reconstruction or revision of existing breast implants for medical or surgical complications. In June of 1998, FDA approved Inamed's IDE study for their Core Study of augmentation, reconstruction, and revision indications.

B. Summary of Clinical Studies

The sponsor reports data from 4 clinical studies: the Core Study, Adjunct Study, AR90 Study, and the SEER (Surveillance Epidemiology End Results Registry) study. The Core Study, Adjunct Study, and AR90 Study are prospective studies. The Core Study, initiated in 1999, reports on approximately a total of 940 augmentation, reconstruction, and revision patients, with yearly follow-up intended to 10 years after implantation. The Core Study is the only study in which detailed local complications and effectiveness information is collected, and the only study in which a subset of approximately 34% of the patients underwent serial screening via MRI for the determination of asymptomatic (i.e. silent) rupture. It constitutes the major clinical information in support of safety and effectiveness. The Adjunct study began in 1998 and was intended to make the implants available for reconstruction and revision patients, while collecting limited safety information at years 1, 3, and 5 after implantation. It provides supportive information on a more limited number of safety outcomes and for the indications of reconstruction and revision only. The AR90 Study, a prospective study with yearly follow-up to 5 years, enrolled predominantly augmentation patients, and because the devices and surgical practices used in this study are no longer current, the data from this study are only briefly summarized. The SEER Registry Study is a retrospective study of breast implant failure in a cohort of breast cancer patients from 3 SEER sites and reports on implants from manufacturers other than Inamed. The data from the SEER are summarized in the "Summary Panel Memorandum."

C. Product Description

The silicone gel-filled breast implant is composed of a shell, silicone gel filler material, and a patch. The **shell** is composed of multiple layers of a high temperature vulcanized silicone co-polymer elastomer (polydimethyldiphenylsiloxane) and is made by sequential dippings of mandrels into dispersed elastomer in solvent and heat curing. An inner layer consists of a higher percentage of diphenylsiloxane in the co-polymer, and is intended to decrease diffusion of silicone gel fill (i.e. to reduce "gel bleed"). Texturing of the shell is accomplished by adding additional layers of coating, followed by a layer of dry salt crystals and additional layers of coating. After curing, water and mechanical abrasion are used to dissolve the salt crystals, which results in the textured surface. Minimum shell thickness ranges from 0.013" for smooth implants to 0.018" for textured shells. Maximum shell thickness ranges from 0.04" for smooth and 0.06" for textured shells. The sponsor refers to the textured implants as BIOCELL®.

When fully cured, the shells are removed from the mandrel. The hole in the shell is covered with a **patch** (also composed of silicone elastomer) on the posterior surface, which is vulcanized (using heat and pressure) to the hole. The **gel filler** is composed of linear and platinum-catalyzed

crosslinked PDMS siloxane polymers. In order to fill the shell, an opening is made in the patch rim with a needle, and the gel is injected into the shell. After filling, the needle hole is sealed with silicone adhesive or another dip coat.

Table 1 below summarizes the characteristics of the various styles of implants for which the sponsor is seeking approval. All are single lumen except for style 153, which consists of two gel-filled lumens. Implant sizes range from 80 cc to 800 cc. Contoured implants, style 153, have a larger inferior projection compared to the superior projection. The sponsor refers to the contoured shape as "shaped."

Table 1: Summary of Implant Styles

Style Number	Shape	Surface	Number of Lumens
10	round	smooth	1
20	round	smooth	1
40	round	smooth	1
45	round	smooth	1
110	round	textured	1
120	round	textured	1
153	contoured	textured	2

II. SUMMARY OF STUDY PROTOCOLS

This section summarizes the clinical protocols for the sponsor's 2 major prospective clinical studies: Core Study and Adjunct Study. The AR1990 study is briefly summarized in Section VIII. of this review: "1990 Study Summary."

A. Core Study Protocol

This open label, prospective study of Inamed (formerly McGhan Medical) silicone gel-filled breast implants was designed with a total of 10 years of follow-up, with at least two years of follow-up obtained prior to submitting a PMA, which is consistent with FDA's Guidance on Breast Implants. Scheduled follow-up visits are at 0-4 weeks, 6 months, 1 year, and then yearly to ten years, following implantation.

Females, aged 18 years or older seeking **primary augmentation** (indications include dissatisfaction with size or shape of breast, asymmetry, ptosis, and aplasia); **primary reconstruction** (indications include mastectomy for cancer, prophylactic mastectomy, breast trauma resulting in mastectomy, and contralateral mastectomy during mastectomy or during placement of permanent implants; primary is defined as no previous implant surgery other than tissue expander); or **breast implant revision** surgery (defined as removal and replacement following previous augmentation or reconstruction with silicone or saline-filled breast implants) and with adequate tissue cover were included. Patients with the following conditions were **excluded**: advanced fibrocystic disease considered to be premalignant without accompanying subcutaneous mastectomy; existing carcinoma of the breast without mastectomy; abscess or infection; pregnant or nursing; diseases, such as uncontrolled diabetes, which are known to impact wound healing; tissue characteristics--such as tissue damage from radiation, inadequate tissue, compromised vascularity, or ulceration—which are incompatible with mammoplasty;

conditions which constitute an unwarranted surgical risk such as unstable cardiac or pulmonary problems; psychological characteristics such as inappropriate attitude or motivation; and, patients unwilling to undergo revision surgery, if indicated.

The **sample size** of 940 patients (500 for augmentation, 220 for reconstruction, and 220 for revision) was based on estimating the precision around the 95% confidence interval of a possible complication event rate. Assuming a drop out rate of 20% at 2 years and of 40% at 10 years, the precision around the 95% confidence interval was estimated to be approximately ± 2% for augmentation at 2 years for a complication rate of 1%, and a precision of ± 4% for reconstruction or revision at 2 years for a complication rate of 1%. For a more commonly occurring complication at the 50% rate, the study was powered for a precision of ± 10% at 2 years for augmentation and ± 15% for reconstruction/revision at 2 years. At 10 years, the respective precision values are slightly higher than at 2 years. This sample size estimate is consistent with guidance provided by FDA in its Guidance Document on Breast Implants.

The **primary safety evaluations**, which were assessed at each follow-up visit, were for local complications. **Secondary safety** evaluations included general medical diseases, lactation history, reproduction history, abnormal mammography, breast diseases, medications, and reports of connective tissue disease diagnosis. An Activities and Lifestyle index, which assessed pain, physical function, and a variety of medical signs and symptoms, was additionally scheduled to be collected at years 1, 2, 4, 6, 8, and 10. If the patient reported a diagnosis of connective tissue disease, or if the signs and symptoms on the Activities and Lifestyle index suggested a possible connective tissue disease, the investigator could refer the patient to a rheumatologist for additional diagnostic follow-up and testing.

As another primary assessment of safety **screening for asymptomatic (i.e. silent) rupture via MRI**, was performed in a subset of 150 augmentation, 101 reconstruction, and 73 revision patients, who were to undergo serial MRI screening for silent rupture at years 1, 3, 5, 7, and 9. This sample size was based on estimating the precision around the 95% confidence interval of a possible silent rupture event rate. The sample size was based on estimating a precision of ± 2.5% for a 5% device silent rupture rate at 9 years, and assuming a 60% drop out rate at 9 years (and a 15% drop out rate at 1 year), which necessitated enrollment of 525 total devices. Assuming an overall sample ratio of 50%/25%/25% augmentation/reconstruction/revision, and assuming 2.0 devices/patient for augmentation, 1.3 devices/patient for reconstruction, and 1.8 devices/patient for revision, the sample size was obtained. MRI examinations were to be performed at centers with a dedicated breast coil, with readings by the local facility sent to the investigator. The MRI images were sent to a Central MRI Reviewer, who was to be blinded to the local facility's evaluation. The Central Reviewer was to provide a report to the investigator and to the sponsor. The investigator, upon review of the local and the Central MRI results, was to consult with the patient on the appropriate treatment or follow-up evaluation.

Effectiveness assessments included breast measurements in augmentation patients, and quality of life (at years 1, 2, 4, 6, 8, and 10) measures of SF-36, MOS-20, Body Esteem Scale, Rosenberg Self Esteem, and Tennessee Self Concept Scale.

B. Core Study Data Reporting

For follow-up compliance data reporting, the sponsor used an additional 2 months for determining when a patient was past their theoretically due timepoint. For complications, the timepoint reported by the patient or determined by the physician was used to report the timepoint of complication occurrence. For the endpoints reproduction and lactation problems, breast disease, connective tissue/autoimmune disease, and patient satisfaction, "through 2 years" is inclusive of all results obtained from 18 through 30 months due to a 6 month "window" around the 2 year time point, and likewise, "through 3 years" is inclusive of ± 6 months.

Note that if a patient underwent unilateral implantation and subsequently underwent contralateral implantation, then on a by-patient basis, all analyses are based on the first implant date. By-implant analyses are based on the separate dates for each of the implantations. If a patient underwent explantation of all study implants without reimplantation, that patient was considered discontinued from further follow-up. The sponsor was encouraged to continue to follow such patients. However, follow-up is limited in these cases as patients often exited the study. Patients who underwent replacement (i.e. secondary implantation) with study implant(s) continued to have follow-up information collected; however, this information was reported separately from the primary implantation data.

The sponsor provided as secondary analysis methods, prevalence, which is based on all patients/implants in which the event is experienced, and incidence, which is the number of new patients/implants who experienced the event since the last follow-up time point. The sponsor indicates that the denominator used for these secondary analyses is based on the number of patients/implants evaluated at a time point, and that this number is assumed to apply to all previous visits. I could not confirm the incidence and prevalence values reported by the sponsor using either expected or actual patients seen; therefore, I will not be summarizing this information.

With respect to local complications, the sponsor collected **severity ratings** (very mild, mild, moderate, severe, or very severe) for all local complications. In the original PMA submission, with the exception of extrusion and pneumothorax, incidence and risk rate data was provided only for those events rated moderate, severe, or very severe. Deficiency #10 of FDA's March 21, 2003 major deficiency letter asked the sponsor to utilize the same reporting method as that used in the product labeling for saline-filled breast implants, wherein only for the complications of asymmetry, breast pain, palpability, visibility, malposition, irritation/inflammation, wrinkling, loss of nipple sensation, nipple paresthesia, delayed wound healing, capsule calcification, and skin paresthesia, only complications with ≥ moderate severity were reported. Deficiency # 11 of FDA's March 21, 2003 major deficiency letter asked the sponsor to combine categories of similar complications or to re-define categories into those currently utilized in the labeling for the approved saline-filled breast implant labeling. The information requested in deficiencies #10 and #11 was provided by the sponsor in Amendment 3, and it is reflected in the tables to follow in this review.

The sponsor defined a **reoperation** as a visit during which at least one secondary procedure was performed involving one or more primary study devices. A given patient may have had more than one reoperation, and more than one secondary procedure may have been performed during each reoperation. If more than one reason for reoperation was given, then, a hierarchy was used

to report the primary reason with device-related complications having higher status than non-implant related complications. The sponsor was asked in deficiencies #4 and #6 of FDA's March 21, 2003 major deficiency letter to provide revised hierarchies which were consistent with that used for reporting hierarchy in the saline-filled breast implant labeling. This was provided in Amendment 3, and it is reflected in this review. The **hierarchy for reporting primary reason for reoperation** is as follows: device malfunction/rupture, infection, capsular contracture, implant extrusion, necrosis, healing related (with the exception of extrusion/necrosis, including swelling), pain, unsatisfactory cosmetic result, device injury (iatrogenic or traumatic), breast cancer, biopsy, patient request, and other. This **same hierarchy** was used to present the **implant removal/replacement** data.

With respect to **reporting possible implant rupture** for the Core Study, the sponsor included data from three sources: (1) the check box "suspected rupture" on the Complications Case Report Form; (2) evidence of rupture noted at explantation or at reoperation and recorded on the Explant Case Report Form; and, (3) for the subset of approximately 34% of the Core Study patients participating in the serial MRI screening evaluation for silent rupture, those devices reported as "ruptured" or "indeterminate for rupture" by either the Local or Central MRI reader and recorded on the MRI Results Case Report Form.

Most implants initially suspected of rupture by one of the above three methods underwent additional testing (i.e. implant replacement/removal, subsequent MRI screening, follow-up ultrasound) in an attempt to confirm the rupture status of the implant. The sponsor reports implants as "confirmed as ruptured" if the rupture was evident at the time of implant replacement/removal. **Therefore, only those implants noted to have visible rupture by the explanting physician at the time implant removal/replacement were reported as "confirmed rupture" by the sponsor.** The sponsor reports "unconfirmed ruptures" if rupture is suspected by one of the three sources described above, and a confirmatory follow-up study/procedure (such as a follow-up MRI or implant removal/replacement) has not been performed. The sponsor reports implants as "not ruptured" if at implant removal/replacement, the physician reported no visible evidence of rupture, or, in the case of rupture noted on MRI, a subsequent serial MRI examination or subsequent MRI reading indicated no rupture.

As part of the **Device Retrieval Study**, all removed implants (from all prospective studies, including the Core Study) were to be returned to the sponsor for microscopic evaluation. Note that not all of the implants suspected of rupture and explanted were returned to the sponsor for this microscopic evaluation. Therefore, some of the implants removed/replaced and noted to not have visible evidence of rupture by the explanting physician may have had microscopic evidence of rupture.

For symptomatic ruptures (i.e. those noted by physician examination) the onset of symptoms is used in the Kaplan-Meier analyses for **determination of the onset of rupture**. For ruptures identified via reoperation/explantation, or for asymptomatic ruptures identified by MRI screening of a subset of the Core Study patients, because the exact date of occurrence of rupture is unknown, the onset time is estimated by the sponsor as halfway back from the time of reoperation/explantation/MRI to the last date the implant was known to be intact.

C. Core Study Conduct

There were a total of 92 protocol violations in the Core Study. The majority of these involved patients signing an informed consent document with no or incorrect IRB information or signing an informed consent document that had missing historical device rupture rate information. In the latter case, the patients were provided the correct rupture rate information at their next scheduled follow-up visit. ***These are minor deviations***.

D. Adjunct Study Protocol

This study, a prospective open-label study, was initiated in 1998, and was intended to make the implants available for patients seeking primary breast reconstruction or revision of an existing implant due to medical or surgical complications, while collecting limited safety information up to 5 years after implantation. The **indications for use** for this study are patients who meet the inclusion/exclusion criteria for reconstruction or revision of an existing breast implant with silicone gel-filled breast implants. The **inclusion criteria with respect to this indication** includes any of the following conditions: post mastectomy surgical removal of the breast for cancer or other diseases; post trauma or post surgery (for any reason) with total or partial removal of the breast resulting in significant deformity; severe ptosis requiring reconstruction (i.e. mastopexy); any congenital or acquired discrepancy in breast size which represents a significant physical deformity including but not limited to pectus excavatum, pectus carinatum, thoracic hypoplasia (Poland's syndrome), scoliosis, tuberous breasts, or congenital absence; revision of an existing (saline-filled or silicone gel-filled) implant due to a problem such as implant rupture or significant capsular contracture (Baker Grade III or IV) requiring revision; or, contralateral mammoplasty for one of the aforementioned circumstances, when medically indicated to provide symmetry. **Additional inclusion criteria** include the following: females of any age for which breast reconstruction is considered appropriate, adequate tissue cover, and saline-filled implants are not an appropriate choice.

Exclusion criteria include the following: advanced fibrocystic disease considered to be premalignant without accompanying subcutaneous mastectomy; existing carcinoma of the breast without mastectomy; abscess or infection in the body at the time of enrollment; pregnant or nursing; any disease, including uncontrolled diabetes, which is clinically known to impact wound healing ability; tissue characteristics which are clinically incompatible with mammoplasty (such as tissue damage resulting from radiation, inadequate tissue, compromised vascularity, or ulceration); unwarranted surgical risk; inappropriate attitude or motivation; augmentation mammoplasty without at least one of the inclusion criteria pertaining to the indication; diagnosis of lupus or scleroderma; and, replacement of saline-filled implants solely for a less than desirable outcome, such as wrinkling.

Sample size is not limited in this study, in keeping with the intention of making these implants available for patients perceived to have a public health need, and enrollment is currently ongoing. **Implant styles** included in this study are Styles 10, 20, 40, 45, 110, 120, and 153, which are included in the styles for which the sponsor is seeking approval. **Follow-up** frequency is pre-operatively, intra-operatively, and at one, three, and five years post-operatively.

The **complications collected at follow-up** include the following: swelling, redness, breast pain, bruising, loss of nipple sensation, nipple hypersensitivity, skin paresthesia, skin hypersensitivity, delayed wound healing, irritation, wrinkling, implant malposition, asymmetry, implant palpability, implant visibility, capsule calcification, hematoma, seroma, infection, tissue or skin necrosis, hypertrophic scarring, skin rash, lymphadenopathy, implant extrusion, implant rupture, Baker Grade capsular contracture. With the exception of capsular contracture, all complications were to be recorded in terms of severity: very mild, mild, moderate, severe, and very severe. **Additional information collected at follow-up** includes the following: presence/absence of normal/abnormal mammogram, reproduction/lactation history, medication use, medical history, patient and physician satisfaction, indications for additional procedures, and types of additional procedures performed.

E. Adjunct Study Conduct

Protocol deviations included the following: informed consent for Adjunct Study not obtained prior to surgery (211 patients); IRB suspension (4 investigators); device implanted at a facility without IRB approval (86 patients); patient not eligible due to inclusion/exclusion criteria violations (26 patients); and, device implanted by a non-authorized investigator at an IRB approved site (25 patients). Note that these violations do not affect the quality or the quantity of the data. Of the protocol violations, 23 met no valid inclusion criteria (i.e. augmentation indication), 1 patient was pregnant, and 2 were transgender patients. Safety data from these patients was excluded from the complication presentation.

Of those protocol deviations in which surgery was performed prior to obtaining informed consent for the Adjunct Study (211 patients), the sponsor obtained signed informed consent documents for all except 27 patients. The sponsor indicates that shipment of Adjunct Study Devices has been suspended at these sites until adequate resolution of the protocol violations and signed informed consent documents for the Adjunct Study are provided. The sponsor indicates that in some cases, patients who do not wish to participate in the Adjunct Study have refused to sign the informed consent document for this study.

III. CORE STUDY RESULTS--AUGMENTATION

A. Patient Disposition—Core Augmentation Cohort

Enrollment of the augmentation cohort occurred between January of 1999 and June of 2000 by 20 investigators at 23 sites. Most of the investigators are in private practice as opposed to academic institutions. Investigators enrolled as few as 2 and as many as 46 patients. Most investigators implanted one or two of the 7 styles for which the sponsor is seeking approval. Note that styles 10 and 20 (smooth surface, moderate and full projection, respectively) were not utilized in this cohort. The least used style was 153, double lumen contoured.

The date of **database closure was March 27, 2003**; therefore, 2 years of follow-up is available for all patients, with some patients having up to 4½ years of follow-up. Based on this date, 83.0% of patients were eligible for a 3 year (+2 months) visit. A total of **495 augmentation patients were implanted**. One patient was excluded from the analyses due to violation of the inclusion criterion of age 18 years or older; therefore, **data are reported for 494 patients (987 devices).** Through 3 years (up to 42 months), there were **19 patients who were known to have**

discontinued from the study: 1 due to death (no information given; obituary reported without cause of death), 5 due to patient choice (i.e. long travel distance or refusal of further follow-up) and 13 due to removal without replacement of all study implants.

Of the 13 patients (26 implants)who underwent removal without replacement of both study implants through 3 years (42 months), 4 patients requested a change to saline implants, 3 patients no longer wanted the implants, 3 patients underwent replacement with another manufacturer's implants, and for 3 patients, an unknown reason was given for not replacing with study implants. Of note, most of these patients reported at least one, and in most cases, several complications; 3 of these patients reported no complications (one patient wanted larger implants, one wanted saline, and one reporting no longer wanting the implants). Of the 10 patients reporting at least one complication, using the hierarchy for implant removal, the **primary reason for implant removal in these discontinued patients** is as follows: capsular contracture (5 patients), swelling (2 patients), wrinkling/rippling (1 patient), asymmetry (1 patient), and heaviness in implants (1 patient). Note that the sponsor did include these complications in the reporting of KM risk rates.

Table 2 below summarizes patient disposition through 3 years. The **follow-up rate through 3 years** (which is **actual divided by expected follow-up) is 81.3%**. The two year follow-up rate (data not shown) is 90.1%, which is excellent. Note that the sponsor used a +2 month window for determining those patients theoretically due; yet, they used a +6 month window for reporting cumulative deaths and explants. Because it is important to include all known reported deaths and explants in the reporting of patient disposition, Table 2 below includes data with these inconsistent timepoints and an explanation in the footnotes.

Table 2: Patient Disposition through 3 years on a by-patient basis—Core Augmentation Cohort.

N = 494 patients enrolled[1] N = 987 devices enrolled	
Theoretical follow-up[2]: N = 410 patients Expected follow-up[3]: N = 396 Actual follow-up: N = 322 (81.3%)	
Withdrawals N = 76	
Reason for withdrawal	Number of patients withdrawn
Death[4]	1
Implant removal[4,5]	13
Lost to follow-up[6]	62

Notes: [1]Excludes one patient who did not meet inclusion criterion for minimal age of 18 years at implantation.
[2]Based on follow-up to 38 months due to an additional 2 month window for the 3 year follow-up visit to determine theoretically due.
[3]Expected follow-up is theoretical follow-up minus deaths and removals without replacement.
[4]Based on follow-up to 42 months due to an additional 6 month window for determination of deaths and removals.
[5]Defined as removal without replacement of all study implants: 4 due to replacement with saline implants, 3 due to no longer wanting implants, 3 due to replacement with another manufacturer's implants, and 3 with no reason given. Note that 10 of these patients reported at least one complication.
[6]Five of these patients requested discontinuation from the study due to long travel distance or refusal of follow-up.

B. Demographics/Baseline Characteristics—Core Augmentation Cohort

The demographic and baseline characteristics are summarized in Table 3 below. The **median age is 34 years** (range 18 to 60 years). Note that the American Society for Aesthetic Plastic Surgery in 2001 indicates that the majority of breast augmentation patients are **between the ages of 19 and 50 years old, which is significant in representing the reproductive years.**

Table 3: Patient demographic and baseline characteristics—Core Augmentation

	Augmentation N = 494 patients
Median age (range) in years	34 (18-60)
Number (%) Caucasian	415 (84.0%)
Median weight (range) in pounds	125 (90-200)

The surgical setting, type of anesthesia used, distribution of implant types used, incision site, implant location, and intraoperative medication use is summarized in Tables 4 and 5 below. Most patients underwent implantation in an outpatient basis, had general anesthesia, and had parenteral medication (most commonly antibiotic). There were no surgical complications reported. **Drains** were placed in only 18.6% of implantations, and concurrent procedures were

performed in only 146 (14.8%) of implantations. Of these 146 implantations with concurrent procedures, the majority 128 (87.7%) consisted of **mastopexy**.

The majority of implants (68.3%) were placed in submuscular location. The use of smooth versus textured implants was nearly approximately equal: 55% smooth and 45% textured. The majority of implants (92.3% of implants) were placed with some type of pocket irrigation. The most common type of pocket irrigation was with an antibiotic.

Table 4: Surgical setting, anesthesia, and parenteral medication—Core Augmentation

	Augmentation N = 494 patients
Type of Facility	
• Doctor's Office	• 235 (47.6%)
• Surgical Center	• 196 (39.7%)
• Hospital	• 63 (12.8%)
Type of Anesthesia	
• General (± Local)	• 375 (75.9%)
• Local Only	• 119 (24.1%)
Parenteral Medication[1]	
• Antibiotics	• 424 (85.8%)
• Steroid	• 152 (30.8%)
• Anesthetic	• 2 (0.4%)
• Sedative	• 48 (9.7%)
• Other	• 21 (4.3%)
• None	• 67 (13.6%)

Notes: [1]The sum of parenteral medication exceeds 100% because more than one type of medication may have been used for an individual patient.

Table 5: Surgical characteristics—Core Augmentation

	Augmentation N = 987 implants
Incision Site	
• Inframammary	• 462 (46.8%)
• Periareolar	• 388 (39.3%)
• Axillary	• 124 (12.6%)
• Mastopexy Incision/Breast Scar	• 13 (1.3%)
Implant Location	
• Submuscular-Complete	• 94 (9.5%)
• Submuscular-Partial	• 580 (58.8%)
• Subglandular	• 307 (31.1%)
• Subcutaneous	• 6 (0.6%)
Product Styles	
• Style 40 (Smooth, round)	• 420 (42.6%)
• Style 45 (Smooth, round)	• 120 (12.2%)
• Style 110 (Textured, round)	• 244 (24.7%)
• Style 120 (Textured, round)	• 128 (13.0%)
• Style 153 (Textured, contoured)	• 75 (7.6%)
Surgical Pocket Irrigation[1]	
• Steroid	• 8 (0.8%)
• Antibiotic	• 761 (77.1%)
• Betadine	• 396 (40.1%)
• Local Anesthetic	• 318 (32.2%)
• Not reported	• 2 (0.2%)
• None	• 76 (7.7%)

Notes: [1]The sum of pocket irrigation exceeds 100% because more than one type of irrigation may have been used for an implant.

C. Local Complications—Core Augmentation Cohort

Table 6 below summarizes the 3 year cumulative Kaplan-Meier (KM) risk rates of first occurrence of complications occurring in ≥ 1% patients reported on a by-patient basis.

For the majority of local complication types reported in the Core Augmentation Cohort (i.e. asymmetry, breast pain, bruising, delayed wound healing, hypertrophic scarring, palpability, irritation, lymphadenopathy, nipple hypersensitivity, other abnormal scarring, ptosis, redness, seroma, skin hypersensitivity, swelling, wrinkling/rippling, and other complications), the majority of reports were of very mild or mild severity. There were no reports of irritation or pneumothorax in the Core Augmentation Cohort.

Table 6: By patient cumulative Kaplan-Meier (KM) risk rates of first occurrence (95% confidence interval) of local complications[1] occurring in ≥ 1%[2] through 3 years of follow-up—Core Augmentation Cohort.

	Core Augmentation N = 494 Patients	
Complication	Rate	(95% CI)
Asymmetry[1]	2.8%	(1.3%, 4.4%)
Breast Pain[1]	6.2%	(4.0%, 8.4%)
Bruising	9.3%	(6.7%, 11.9%)
Capsular Contracture III/IV	8.3%	(5.8%, 10.9%)
Delayed Wound Healing[1]	1.1%	(0.1%, 2.1%)
Hematoma	1.0%	(0.1%, 1.9%)
Implant Malposition[1]	3.1%	(1.5%, 4.8%)
Implant Rupture[3]	1.2%	(0.1%, 2.2%)
Infection	1.0%	(0.1%, 1.9%)
Loss of Nipple Sensation[1]	3.1%	(1.6%, 4.7%)
Loss of Skin Sensation	1.2%	(0.3%, 2.2%)
Other Nipple Complication	2.8%	(1.3%, 4.2%)
Ptosis	3.3%	(1.7%, 5.0%)
Redness	2.6%	(1.1% 4.1%)
Removal/replacement	7.5%	(5.0%, 10.0%)
Reoperation	20.6%	(16.8%, 24.4%)
Scarring[4]	8.1%	(5.7%, 10.6 %)
Seroma/Fluid Collection	2.7%	(1.3%, 4.1%)
Skin Rash	3.1%	(1.6%, 4.6%)
Skin Sensation Changes[1,5]	1.7%	(0.5%, 2.8%)
Swelling	23.3%	(19.5%, 27.0%)

Notes: [1]Includes reports of only ≥ moderate severity for the complications of asymmetry, breast pain, capsule calcification, delayed wound healing, implant malposition, irritation/inflammation, loss of nipple sensation, nipple complications, palpability/visibility, skin sensation changes, and wrinkling.

[2]Capsule calcification (0.2%), implant extrusion (0.2%), palpability/visibility (0.6%), lymphadenopathy (0.4%), lymphedema (0.2%), tissue/skin necrosis (0.2%), wrinkling/rippling (0.7%), nipple paresthesia/hypersensitivity (0.8%). and drug reaction to compazine (0.2%) not shown.

[3]Includes confirmed rupture of 2 silicone gel-filled implants in 2 patients detected through explant and 3 suspected yet unconfirmed implant ruptures in 3 patients identified by MRI for a total of 5 implant ruptures in 5 patients. Excludes one implant rupture not confirmed with MRI or explant, and excludes one implant rupture noted to be visibly intact by the explanting physician but having a sharp edge opening on microscopic evaluation (See Figure 1 for details on rupture).

[4]Includes all scarring complications.

[5]Includes all reports of hypersensitivity, paresthesia, and loss of skin sensation.

Reoperation:

With respect to **reoperation**, there were a total of 248 additional surgical procedures performed in 112 reoperations in 94 of the 494 patients (19.1%) through 3 years of follow-up in the Core Augmentation Cohort. On a by-implant basis, 150 of the 987 primary implants (15.2%) underwent at least one reoperation. Of the 94 patients undergoing at least one reoperation, the majority (79 patients, 84.0%) underwent one reoperation; 12 patients (12.8%) underwent 2 reoperations, and 3 patients (3.2%) underwent 3 or more reoperations. Of the 112 reoperations, approximately 75% involved one or two procedures per reoperation. **Table 7** below summarizes the types of reoperation procedures performed through 3 years in the Augmentation Cohort. The two most commonly performed procedures were capsule related (31.9%) and removal with replacement (20.6%).

Table 7: Types of reoperation procedures performed through 3 years--Core Augmentation Cohort.

Type of Procedure	Core Augmentation N = 248 Procedures 3 Years
Removal with replacement	51 (20.6%)
Removal without replacement	9 (3.6%)
Capsulotomy	47 (19.0%)
Capsulorraphy	4 (1.6%)
Capsulectomy	28 (11.3%)
Mastopexy	42 (16.9%)
Scar revision/wound repair	23 (9.3%)
Implant reposition	14 (5.6%)
Biopsy/removal of tissue/lesion/cyst[1]	13 (5.2%)
Pocket revision/exploration of implant area/suture removal	9 (3.6%)
Hematoma/seroma aspiration	5 (2.0%)
Unplanned nipple revision/tattoo	3 (1.2%)

Notes: [1]Includes one case of mastectomy.

Table 8 summarizes the primary reason for reoperation based on the suggested hierarchy described in section II.B. of this review. There were 32 primary replacement/removal reoperations through 3 years; the majority of these (24 reoperations; 75%) were due to a complication—including unsatisfactory cosmetic result, which is a clinically significant complication, particularly for a cosmetic indication—and 8 (25%) were due to patient request. Of the 26 capsule reoperations, capsular contracture/pain constituted the primary reason for the majority of these reoperations (20 of 26; 77%); while, 6 of the capsule reoperations (23%) were due to an unsatisfactory cosmetic result.

Table 8: Primary reason[1] for reoperation and primary procedure performed through 3 years—Core Augmentation Cohort.

Primary Reason	Procedure	Reoperations N = 112
Device Rupture	Replacement/Removal	1 (0.9%)
Capsular Contracture	Replacement/Removal	16 (14.3%)
	Capsule Procedure	19 (17.0%)
Extrusion	Replacement/Removal	1 (0.9%)
Necrosis	Wound Repair	1 (0.9%)
Healing Related	Hematoma/Seroma Aspiration	5 (4.5%)
	Wound Repair/Suture Removal	2 (1.8%)
	Nipple Revision/Tattoo	1 (0.9%)
	Mastopexy	1 (0.9%)
Pain	Capsule Procedure	1 (0.9%)
Unsatisfactory Cosmetic Result	Mastopexy	14 (12.5%)
	Scar Revision	11 (9.8%)
	Capsule Procedure	6 (5.4%)
	Removal/Replacement	5 (4.5%)
	Reposition Implant	5 (4.5%)
	Pocket Revision	3 (2.7%)
	Breast Area/Implant Exploration	1 (0.9%)
Breast Cancer	Replacement/Removal	1 (0.9%)
Need for Biopsy	Biopsy	10 (8.9%)
Patient Request	Removal/Replacement	8 (7.1%)

Notes: [1]Heirarchy: device malfunction/rupture, infection, capsular contracture, extrusion, necrosis, healing related (hematoma/seroma, delayed wound healing), pain, unsatisfactory cosmetic result (contour deformity, malposition, wrinkling/rippling, palpability/visibility, asymmetry, ptosis, scarring), iatrogenic or traumatic injury, breast cancer, biopsy, patient request (style/size change, anxiety), other.

Implant Replacement/Removal:

With respect to **implant replacement/removal**, of the 987 primary augmentation devices implanted, there were 60 implants removed (6.1%) through 3 years for any reason—**Table 9**—which were removed/replaced in 32 reoperations. Of the 60 implant removal/replacements, the majority (42 of 60 implants; 70.0%) were removed/replaced to treat a complication, including those complications categorized as cosmetic, and 30.0% were removed/replaced due to patient request. Of the 494 augmentation patients, 32 patients (6.5%) underwent at least one removal/replacement through 3 years, with 27 patients (51 implants) undergoing replacement, and 5 patients (9 implants) undergoing removal without replacement. Of the 51 implant replacements, 27 (53.0%) were for an increase in implant size.

Table 9: Primary reason[1] for implant replacement/removal through 3 years—Core Augmentation

Primary Reason	3 Years N = 60 Implants Removed
Complication Treatment/Cosmetic Outcome	42 (70.0%)
Rupture	2 (3.3%)
Capsular Contracture	27 (45.0%)
Extrusion	1 (1.7%)
Malposition	6 (10.0%)
Asymmetry	3 (5.0%)
Ptosis	2 (3.3%)
Breast Cancer	1 (1.7%)
Patient Choice	18 (30.0%)
Change Size/Style	13 (21.7%)
Patient Concern[2]	5 (8.3%)

Notes: [1]See section II.B. of this review, "Core Study Data Reporting" under "reoperation" for description of hierarchy.
[2]The sponsor refers to this as "media anxiety."

Compliance for serial MRI screening:
Recall that a subset of the Core Study patients underwent **serial MRI screening** for determination of asymptomatic (silent) rupture. For the Core Augmentation cohort, 166 of the total 494 Core Augmentation patients (331 of the total 987 implants) enrolled in the serial MRI subset cohort screening for asymptomatic rupture. Of this 166 Core Augmentation patient subset, 6 patients had removal of their primary implants prior to the first screening at 1 year after implantation. Of the 160 expected patients, there were 139 patients (87% of expected) who had their first serial MRI screening at approximately 1 year after implantation. At the second MRI screening at approximately 3 years after implantation, 83 patients (64% of the 130 expected) had their second serial MRI screening. At the 3 year screening, 47 patients (36% of the 130 expected) were lost to follow-up. **In summary there were 289 implants in 145 patients which had at least one MRI screening and are included in the MRI subset for Core Augmentation. On a by-implant basis, this represents 29.3 % of the total 987 Core Augmentation implants.** The findings of this screening are described in the "Rupture" section below.

Rupture:
The sponsor was asked to provide reports of all diagnostic studies related to implant rupture, and surgical operation notes of all explantations related to implant rupture. The following summary incorporates this information.

Of the 987 total Core Augmentation implants, **10 implants were initially reported as "suspected" ruptured** through 3 years of follow-up: 1 suspected at physician exam (pain and tenderness following a motor vehicle accident), 2 reported at reoperation, 1 reported at explant, and 6 reported via the **MRI screening subset** (described above) of 289 Core Augmentation implants which underwent at least one MRI screening for asymptomatic rupture following implantation. These "suspected" ruptures, in some cases, underwent additional evaluation, which is depicted in **Figure 1: Flowchart of Ruptures—Core Augmentation** below. The

following text in this section explains the sponsor's characterizations of these suspected ruptures as shown in **Figure 1**.

The one implant suspected of rupture reported by physician exam following a motor vehicle accident underwent mammography and clinical follow-up which indicated an intact implant. Note that although neither explant nor MRI have been performed to definitively rule out a rupture, this implant was reported as "not ruptured" by the sponsor and is not included in the rupture rate.

Of the two implants suspected of rupture reported at reoperation (the reoperation was for Baker grade IV capsular contracture), both implants were in the same patient. At the reoperation--which was capsulectomy and replacement--one implant was reported as having intracapsular rupture and the other was reported as intact by the physician. This latter implant was returned to the sponsor as part of the Device Retrieval Study, and examined microscopically, revealing one "sharp-edge opening," which according to the sponsor, indicates surgical instrument damage. Note that although microscopic analysis indicated a rupture in this implant, because this rupture was not reported at explant, it is not included in the rupture rate.

The one implant suspected of rupture reported at explant was confirmed as an intracapsular rupture. This patient initially complained of pain and nodules in the left breast and axilla. An ultrasound was obtained which indicated fluid around the implant and echogenic nodules in the axilla. At explant, an intracapsular rupture was noted by the explanting surgeon.

Of the **6 suspected implant ruptures identified through MRI screening,** all were asymptomatic and were not clinically evident—considered possibly silent ruptures. Of these 6 possible ruptures via MRI, 4 were determined to be "indeterminate for MRI rupture" by either the Local or Central MRI radiologist, and 2 were determined to have "evidence of MRI rupture". Agreement between the Local and Central MRI radiologists was 90% for the augmentation cohort.

Follow-up evaluation of these **6 possible MRI silent ruptures** is as follows. For the **4 implants rated indeterminate** for rupture at initial MRI screening, 2 had not yet had a confirmatory study by the time of database closure and are classified as "unconfirmed" by the sponsor (a follow-up MRI was performed approximately 1 year after the indeterminate rupture status showing intact implants for these 2 implants; however, this report was received after the database closure date); and subsequent MRI of the other two implants approximately 1 year after the indeterminate reading indicated intact implants. For the **2 implants indicating evidence of rupture** on initial MRI screening, one was confirmed intact by both follow-up ultrasound and subsequent MRI screening approximately 1 year later indicating lack of rupture, and the other was not yet confirmed at the time of database closure (subsequent to database closure, however, this implant, which exhibited a keyhole sign and pulling away from the implant shell, was explanted and an intracapsular rupture was noted). Of the 3 implants which underwent a second MRI examination indicating no rupture (2 which were initially determined "indeterminate" for rupture and 1 which had "evidence" of rupture), the sponsor reports all 3 of these as not ruptured.

The sponsor, therefore, reports confirmed rupture via explantation of 2 implants (both are intracapsular; one rupture was noted during capsulectomy for Baker Grade IV capsular

contracture, and the other rupture reported at explant for pain, axillary nodularity, asymmetry, and capsular contracture following an ultrasound report indicating fluid around the implant), and 3 are reported as unconfirmed by the sponsor.

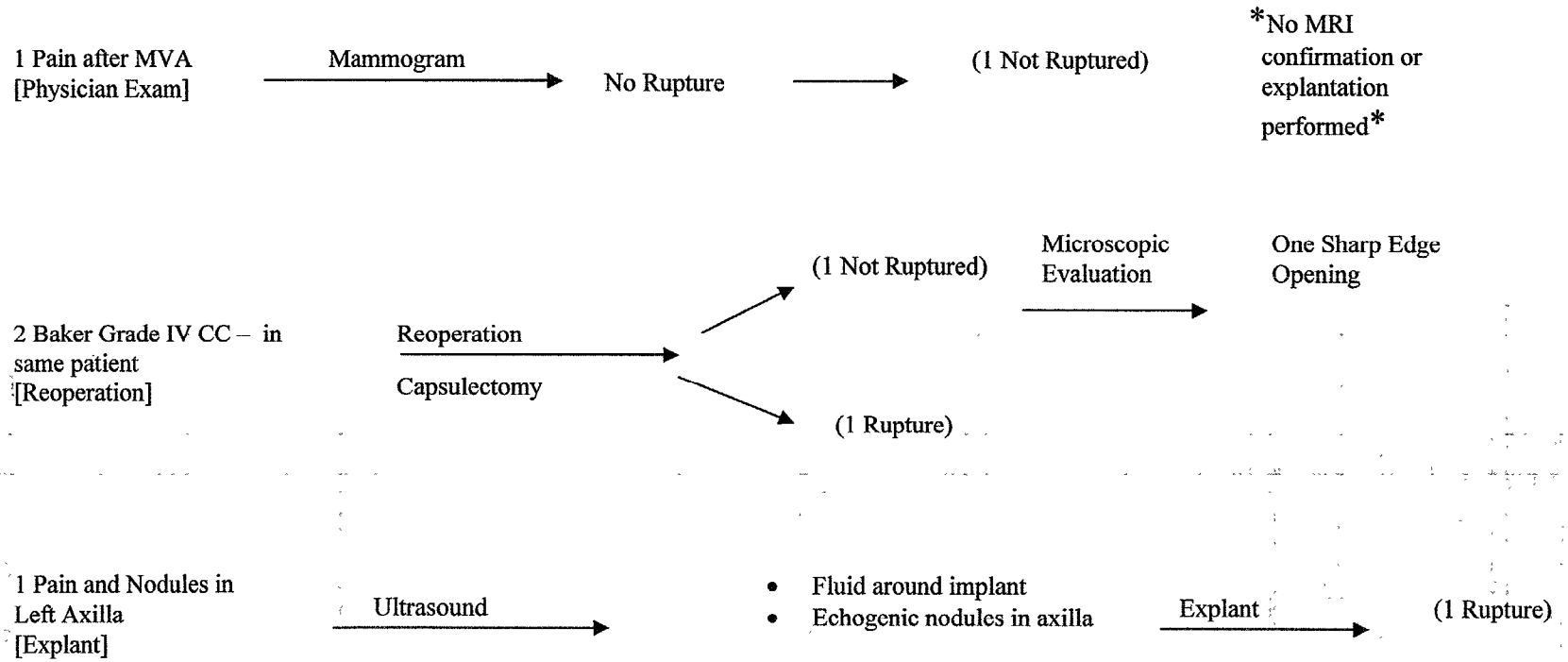
In summary, the rupture rate reported by the sponsor includes **5 implant ruptures--2 confirmed and 3 unconfirmed--in 5 patients through 3 years of follow-up,** with one of the three "unconfirmed" ruptures determined to be ruptured following the database closure date of March 27, 2003. **Of the 2 ruptured implants reported as confirmed by the sponsor, 0 were found via MRI screening; of the 5 total ruptures reported by the sponsor—including those categorized as unconfirmed ruptures—3 were from MRI screening.**

If the additional implant confirmed ruptured after the March 27, 2003 date of database closure is included in the confirmed ruptures, **of the 3 confirmed ruptures by explant, one was asymptomatic and initially identified by MRI screening.**

Recall that less than one-third of the total Core Augmentation implants were included in the MRI screening subset, and that only the first (and partially the second) of 5 serial screenings have occurred. Had the proportion of patients undergoing MRI screening been larger, the rupture rate would likely be larger as well.

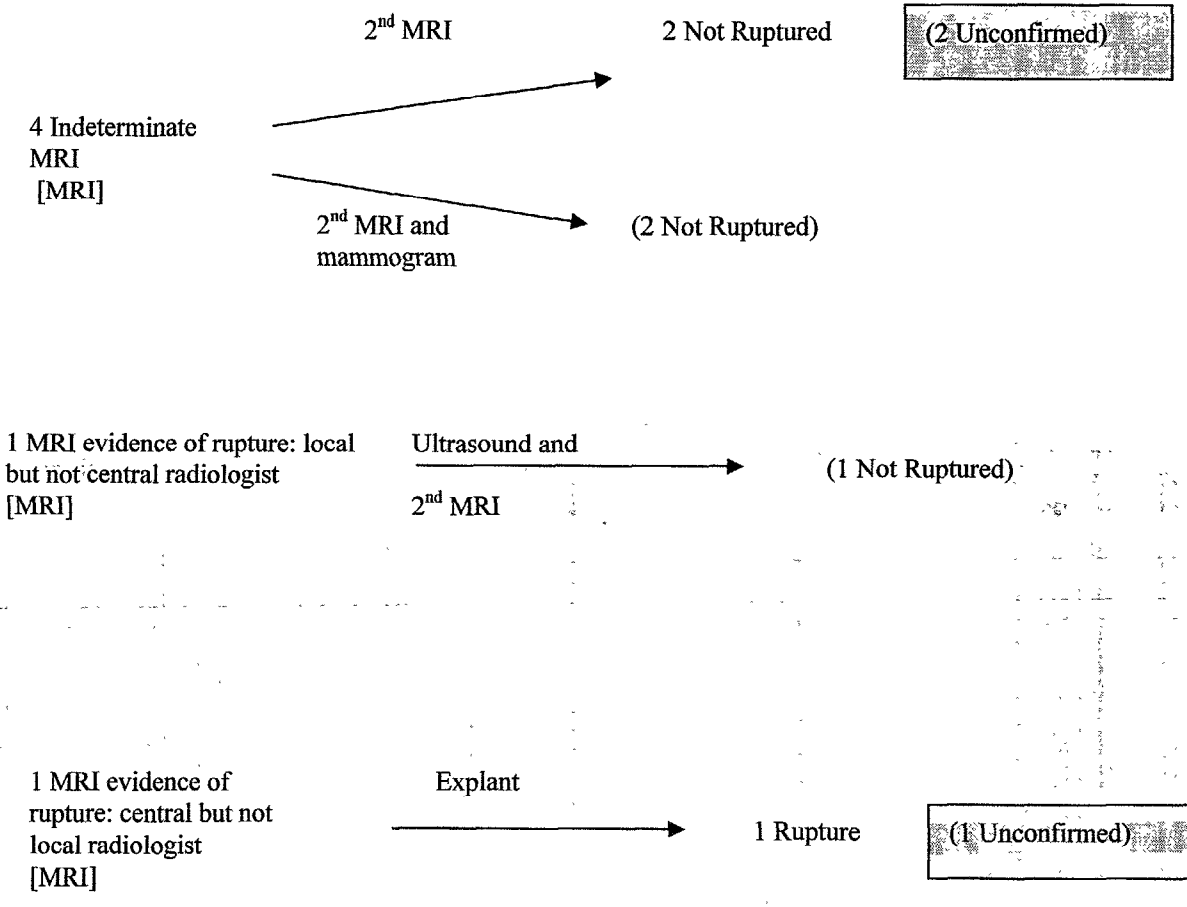
The sponsor reports a 3 year by-implant cumulative Kaplan-Meier **silent rupture rate** of 1.2% (95% CI: 0.0%, 2.6%) based on 3 implant ruptures, highlighted in grey in Figure 1. The 3 year by-implant cumulative Kaplan-Meier **overall rupture rate** (including the 2 implants reported as "confirmed ruptured" and the 3 implants reported as "unconfirmed") is 0.6% (95% CI: 0.1%, 1.1%).

Figure 1: Flowchart of Rupture – Core Augmentation Cohort



Notes: 1. Information in brackets indicates method of initial suspicion of rupture reported by the sponsor.
2. Information in parentheses indicates final rupture status reported by the sponsor. Shading of these represents implants included in determination of silent rupture rate.

Figure 1 (continued): Flowchart of Rupture – Core Augmentation



Summary:

- 5 ruptures in 5 patients
  - 2 ruptured
  - 3 unconfirmed
- Of the 2 confirmed ruptured implants, 0 was found with MRI screening
- Of the total 5 implant ruptures including unconfirmed, 3 were from MRI screening

Notes: 1. Information in brackets indicates method of initial suspicion of rupture reported by the sponsor.
2. Information in parentheses indicates final rupture status reported by the sponsor. Shading of these represents implants included in determination of silent rupture rate.

Complications following implant replacement:
Of the 27 patients (51 implants) who underwent implant removal with replacement through 3 years, **complications following implant replacement** were reported in 16 patients (24 implants): capsular contracture (9 patients), implant malposition (4 patients), ptosis (2 patients), breast pain (2 patients), asymmetry (1 patient), delayed wound healing (1 patient), hypertrophic scarring (1 patient), seroma (1 patient), wrinkling/rippling (1 patient), and other (1 patient). Note that these values are not additive because an implant/patient may have reported more than one occurrence of a complication. Risk rates are not shown because of the small sample size.

D. General Complications—Core Augmentation Cohort

Before breast implantation, 81 of the 494 patients (16.4%) reported the following 94 **reproductive problems**: infertility (20 reports), spontaneous abortion (51 reports), planned abortion (9 reports), ectopic pregnancy (9 reports), hysterectomy (3 reports), endometriosis (1 report), and cervical ligation to treat placenta previa (1 report). Through 3 years after breast implantation, there were 8 patients (1.6%) reporting 9 reproductive problems: 7 reports of spontaneous abortion (one of these patients also had a planned abortion pre-implant), 1 report of ectopic pregnancy, and 1 report of endometriosis. Without information on the number of patients attempting reproduction (which was not collected in the Core Study) and without a comparison group of age-matched patients having cosmetic breast surgery and followed for the same duration, it is not possible to draw definitive conclusions from these data; however, the percentage of patients reporting a problem post-implantation is lower than that pre-implantation. This could be due to less reproductive attempts or to reporting bias.

Before breast implantation, of the 276 patients who attempted to breast feed, 42 patients (15.3%) reported **lactation problems**, with 19 of these patients reporting specifically inadequate milk production (45.2%). Through 3 years after breast implantation, of the 32 patients who attempted to breast feed, 5 patients (15.6%) reported the following 10 lactation problems: 1 report of mastitis not requiring treatment, 2 reports of mastitis requiring treatment, 4 reports of inadequate milk production, 1 report of excessive milk production, 1 report of pain, and 1 report of decreased but still adequate volume of milk. Following implantation, of the 5 patients reporting problems with lactation, 4 patients (80.0%) reported inadequate milk production. Of those women attempting to breast feed, a similar proportion reported problems before and after breast implantation. Of those women attempting to breast feed and reporting problems with lactation, a higher proportion reported inadequate milk production following implantation; however, the numbers are small and may, therefore, be unreliable.

Prior to breast implantation, there were 30 of 494 patients (6.1%) who reported **breast disease**, with 29 of these reported as benign and 1 reported as possible cyst requiring follow-up, which had not been done. Through 3 years, there were 32 patient reports of post-implant breast disease: 1 confirmed malignant, 29 confirmed benign (i.e. fibrocystic disease, cyst, or other benign breast mass or lump), and 2 unconfirmed (2 patients reporting a breast lump on breast self examination but diagnostic mammogram not yet performed at the time of database closure). Of the 29 benign breast disease reports post-implant, in 2 patients, benign breast disease was reported pre-implant in the same breast. The incidence of benign breast disease in Core Augmentation cohort following breast implantation is 29 of 494 patients (5.9%). The incidence of benign breast disease reported in the Nurses Health Study **(Webb, et al., 2002)** is 3.9%.

The one **breast malignancy** occurred 27 months following breast implantation in a 39 year old patient with no family history of breast cancer. The patient initially observed lumps during breast self-examination with biopsy confirming invasive ductal adenocarcinoma in situ (tumor size was 1-2 cm with unknown differentiation reported) with 1-3 nodal involvement. The implant was removed, mastectomy was performed, and no new implant was placed. The incidence of breast cancer in the Core Augmentation cohort following breast implantation is 1 of 494 patients (0.2%). The incidence rate for invasive breast cancer is 0.13% and for breast cancer in situ is 0.03%, as reported by the **U.S. Cancer Statistics Working Group in 2002.**

Prior to implantation, 185 of the 494 patients had a pre-implant **mammogram**. The readings were normal or benign in 184 of these, and in 1 case, follow-up was requested for a suspected cyst, but the patient did not obtain a follow-up mammogram. Through 3 years of follow-up, 151 of the 494 patients had a mammogram, of which 12 were reported abnormal through 3 years without such a report at baseline. Of the 12 abnormal mammogram results, additional follow-up indicated that 1 had no breast disease and 11 had benign breast disease. Of the 11 post-implant benign mammogram reports, one patient had an abnormal mammogram which was benign reported in the same breast pre-implant. Note that this is a young, healthy cohort of patients who may not have had a screening mammogram at either pre-op or post-op.

With respect to **connective tissue/autoimmune disease (CTD)**, the sponsor reported one new post-implant report of a CTD through 3 years of follow-up: a 46 year old patient with rheumatoid arthritis with an onset date of 11 months following breast implant surgery. The sponsor was asked to provide the physician notes and results of laboratory tests pertaining to this diagnosis. Review of this information indicates a diagnosis of non-specific "arthritis" with noted complaints of pain in the patient's hands and right hip, a negative rheumatoid factor, and treatment consisting of celecoxib on a PRN basis. Based on the information provided, a diagnosis of RA is unlikely in this patient.

Recall that the sponsor collected **CTD signs and symptoms** from the patients at baseline and at 1, 2, 4, 6, 8, and 10 years in the Activities and Lifestyle questionnaire to assist in determining CTD diagnoses, if present. This self-administered questionnaire includes a Modified Health Assessment Questionnaire (MHAQ), which assesses ability to perform various physical functions of daily living, and it includes a variety of signs and symptoms related to rheumatic diseases and to general health. Of the 494 Core Augmentation patients, data are available for 385 patients (77.9%) for the MHAQ and for 386 patients (78.1%) for the signs and symptoms. These data are summarized in **Table 10** below. Recall that the intention of this questionnaire is to identify patients who warrant additional evaluation and referral to a rheumatologist. Without a control/comparison group of patients without implants followed for the same duration of follow-up and with similar demographic characteristics, conclusions cannot be made from these data.

Table 10: Summary of signs/symptom categories and selected signs/symptoms through 2 years after implantation—Core Augmentation.

Sign/Symptom Category	Pre-implant N = 386	Through 2 years post-implant N = 386
Skin[1]	29 (7.5%)	50 (13.0%)
Muscle[2]	75 (19.4%)	108 (28.0%)
Joint[3]	50 (13.0%)	85 (22.0%)
Neurological[4]	158 (40.9%)	180 (46.6%)
General[5]	60 (15.5%)	99 (25.6%)
Other[6]	52 (13.5%)	59 (15.3%)
Gastointestinal[7]	101 (26.2%)	119 (30.8%)
Urinary[8]	3 (0.8%)	11 (2.8%)
Muscle weakness	0 (0%)	12 (3.1%)
Muscle pain/aches/cramps	34 (8.8%)	57 (14.8%)
Joint Pain	10 (2.6%)	26 (6.7%)
Morning Stiffness	39 (10.1%)	70 (18.1%)
Fatigue in past week	27 (7.0%)	58 (15.0%)
Fatigue in past month	6 (1.6%)	43 (11.1%)
Pain	8 (2.1%)	19 (4.9%)

Notes: [1]Includes hair loss, skin rash, facial swelling, ecchymosis, purpura, unusual bruising, unusual bleeding, hives, other skin problem.
[2]Includes muscle weakness, muscle pain/aches/cramps, back pain, neck pain.
[3]Includes joint pain, swelling of hands, swelling of other joints, morning stiffness.
[4]Includes memory problems, problems with thinking, headaches, numbness/tingling of arms/legs, losing balance, ringing in ears.
[5]Includes fever, swollen glands, weight loss, weight gain, fatigue, generalized pain.
[6]Includes dry eyes, other eye problems, sores in mouth, dry mouth, problems with taste, trouble swallowing.
[7]Includes heartburn, stomach pain/cramps, nausea, vomiting, constipation, diarrhea, dark stool, blood in stool, loss of appetite, and moderate or greater gastrointestinal trouble.
[8]Includes urinating too often, problems with urination.

E. Additional Analyses of Safety Data—Core Augmentation Cohort

The sponsor performed Cox proportional hazards regression analysis to determine whether the complications of reoperation, implant replacement/removal, implant rupture, capsular contracture, and infection were associated with patient age (≤40 years vs. >40 years), antibiotic pocket irrigation (yes vs. no), betadine pocket irrigation (yes vs. no), implant placement (submuscular vs. other), incision site (periareolar vs. inframammary vs. axillary vs. other), device texture (smooth vs. textured), and device shape (round vs. contoured), as suggested in FDA's Guidance document on Breast Implants. This information is based on an earlier date of database closure of August 30, 2002.

Findings are summarized in **Table 11** below. The "other" incision site shown to be associated with reoperation is mastopexy incision/breast scar and constituted only 1.3% of the augmentation

implants enrolled and only 6 of the 125 implants (4.9%) which underwent reoperation as of August 2002. Lack of pocket irrigation with antibiotics (which involved 22.9% of the enrolled implants and 15 of the 41 explanted implants) was associated with implant removal/replacement. Lack of pocket irrigation with betadine (which involved 59.9% of the enrolled implants and 31 of the 41 explanted implants) was also associated with implant removal/replacement. Smooth surfaced implants (which involved 54.8% of enrolled implants and 34 of 41 explanted implants) were associated with implant removal/replacement.

Table 11: Summary of risk factor analysis—Core Augmentation Cohort

Risk of Complication	Factor	Adjusted Risk Ratio (95% CI)
Reoperation	Other vs. periareolar incision	5.7 (2.4, 13.3)
Reoperation	Other vs. inframammary	5.3 (2.3, 12.3)
Reoperation	Other vs. Axillary	4.4 (1.8, 11.2)
Removal/Replacement	No antibiotic pocket irrigation vs. yes	2.6 (1.3, 5.0)
Removal/Replacement	No Betadine pocket irrigation vs. yes	2.8 (1.3, 5.8)
Removal/Replacement	Smooth vs. Textured	4.3 (1.9, 9.8)

F. Effectiveness—Core Augmentation Cohort

With respect to **breast size**, most patients increased by 1or 2 cup sizes. Approximately 6% of patients experienced no change or decreased breast size due to correction of congenital asymmetry or change in shape without change in size.

The sponsor collected both patient and physician satisfaction. Because the patient satisfaction is more relevant, I will omit the summary of physician satisfaction information. The sponsor collected both general patient satisfaction and satisfaction based on pre-operative expectation of satisfaction. With respect to **general patient satisfaction**, of the 425 patients (of 494) who completed this questionnaire at 2 years, there was a small decline in mean satisfaction from the 0-4 week follow-up timepoint of 4.9 (SD 0.3) to 4.8 (SD 0.7) at 2 years. With respect to patient satisfaction compared to pre-operative expectation of satisfaction, of the 351 (of 494 patients) who responded to these questions, most patients reported being satisfied or very satisfied with their implants at 1 and 2 years post-implant. Approximately 2.6% of these patients were very dissatisfied or dissatisfied, and another 2.6% were neutral regarding their satisfaction at 2 years compared to their pre-operative expectation. There were small but statistically significant declines in mean patient satisfaction at both 1 and 2 years compared to pre-operative expectations of satisfaction. The mean pre-operative expectation value of 4.9 (SD 0.4) was compared to 4.6 (SD 0.7) at 2 years.

With respect to the **Health Status Questionnaire (SF-36 and MOS-20),** the core augmentation cohort reported statistically significantly higher levels for all measures at baseline compared to normative values for the general female population. There were small, statistically significant declines in some subscales of these measures in breast implant recipients over time; however, the 2 year values for the augmentation cohort were generally numerically higher than normative values for the general female population (statistical comparison of 2 year augmentation to normative scores was not performed by the sponsor). The results of selected health status

measures are summarized in **Table 12** below. Note that most of the changes, even those that are worse, are small.

Table 12: Summary of selected health status/QOL measures—Core Augmentation Cohort.

Assessment method	Statistically significant change in pre- to 2 year post-implant score	Direction of change
SF-36 Role Emotional	Yes	Worse
SF-36 Role Physical	Yes	Worse
SF-36 General Health	Yes	Worse
SF-36 Pain	No	Worse
SF-36 Social	Yes	Worse
SF-36 Physical	No	Worse
SF-36 Vitality	Yes	Worse
SF-36 Mental Health	Yes	Worse
MOS-20 Health Perceptions	Yes	Worse
MOS-20 Physical Functioning	No	Worse
MOS-20 Social Functioning	No	Worse
MOS-20 Mental Health	Yes	Worse
TSCS Physical Self	Yes	Better
Rosenberg Self Esteem	No	Worse
Semantic Differential	No	Same
Body Esteem-Total Score	Yes	Better
Body Esteem-Sexual Attractiveness	Yes	Better
Body Esteem-Weight Concern	No	Better
Body Esteem-Physical Condition	Yes	Worse

IV. CORE STUDY RESULTS—RECONSTRUCTION

A. Patient Disposition—Core Reconstruction Cohort

Enrollment of the reconstruction cohort occurred between February of 1999 and June of 2000 by 25 investigators at 34 sites. Investigators enrolled as few as 1 and as many as 28 patients. Most investigators utilized one or two of the 7 styles for which the sponsor is seeking approval. Note that styles 10 and 20 were not utilized in this cohort (nor in the core augmentation cohort). The style least used was style 45 (round, smooth), and the most used style was 153 (contoured, textured, double lumen).

A total of **221 reconstruction patients** were implanted and enrolled (361 implants). All of the patients had traversed their 2 year visit. **Table 13 summarizes the patient disposition** through 2 years **(August 30, 2002 date of database closure).** The **follow-up rate** through 2 years (actual divided by expected) is 95.6%, which is excellent. The follow-up rate through 3 years is 90.5% (not shown), is also excellent. However, because reconstruction patient enrollment began after augmentation enrollment, **3 year data (+ 2 months) is available for only 58.4%** of the reconstruction cohort at the **March 27, 2003 date** of database closure, which is why **Table 13** shows 2-year disposition. Note that the sponsor used a +2 month window for determining those patients theoretically due; yet, they used a +6 month window for reporting cumulative deaths and

explants. Because it is important to include all known reported deaths and explants in the reporting of patient disposition, **Table 13** below includes data with these inconsistent timepoints, and an explanation in the footnotes.

Through 3 years (up to 42 months), there were 26 patients who were known to have discontinued from the study: 7 due to death (5 due to breast cancer recurrence, 1 automobile accident, and 1 unknown), 16 patients due to removal without replacement of all study implants (21 implants; 6 bilateral and 9 unilateral patients), 1 due to patient choice (scheduling conflict), and 2 due to patient/physician conflict.

Of the 16 patients (21 implants) who were discontinued due to removal without replacement of study implants **through 3 years (up to 42 months)**, 4 patients underwent replacement with saline or a non-study gel device, 5 patients underwent replacement with another manufacturer's implant, in 6 an unknown reason was given for not replacing with study implants, and 1 patient reported being not satisfied. It is significant to note that all 16 of these patients experienced at least one, and in most cases, several complications. Using the same hierarchy as for implant removal, **the reasons for removal in these discontinued patients** are as follows: rupture (2 patients), infection (1 patient), capsular contracture (5 patients), swelling (4 patients), pain (3 patients), and asymmetry (1 patient). Note that the sponsor included these complications in the KM risk rates.

Table 13: Patient disposition through 2 years on a by-patient basis—Core Reconstruction Cohort.

N = 221 patients enrolled N = 361 devices enrolled	
Theoretical follow-up[1]: N = 221 patients Expected follow-up[2]: N = 203 Actual follow-up: N = 194 (95.6%)	
Withdrawals N = 27	
Reason for withdrawal	Number of patients withdrawn
Death[3]	6
Implant removal[3,4]	12
Lost to follow-up[5]	9

Notes: [1]Based on follow-up to 26 months due to an additional 2 month window for determining theoretically due for the two year visit.
[2]Expected follow-up is theoretical follow-up minus deaths and removals without replacement.
[3]Based on follow-up to 30 months due to an additional 6 month window for determination of cumulative deaths and removal of all implants.
[4]Defined as removal without replacement of all study implants: 4 due to replacement with saline, 3 due to no longer wanting implants, 2 due to replacement with another manufacturer's implants, and 3 with no reason given. Note that all of these patients reported at least one complication.
[5]One patient reported change in physician due to scheduling conflict; two patients reported patient/physician conflict and one of these patients additionally had complications necessitating breast reduction and secondary closure of wound dehiscence.

B. Demographic/Baseline Characteristics—Core Reconstruction Cohort

The demographic and baseline characteristics are summarized in **Table 14** below.

Table 14: Patient demographic and baseline characteristics—Core Reconstruction

	Reconstruction N = 221 Patients
Median age (range) in years	50 (26 – 82)
Number (%) Caucasian	194 (87.8%)
Median weight (range) in pounds	138 (91 – 240)

The procedure performed, surgical setting, type of anesthesia used, distribution of implant styles used, incision site, implant location, and intraoperative medication use is summarized in **Tables 15 and 16**. Most patients underwent implantation at a hospital facility, had immediate reconstruction, had general anesthesia, and had parenteral medication (mostly antibiotic). There was one surgical complication reported: reopened to verify hemostasis—no hematoma noted. Drains were placed in 62.3% of implantations, and concurrent procedures were commonly performed: 253 of 361 implants (70.1% of implants) were placed with 432 concurrent procedures (an implant may have been placed with more than one concurrent procedure). Of the 253 implants placed with 432 concurrent breast procedures, the majority of procedures involved capsule procedures (199 of 432 procedures; 46.1%), nipple reconstruction (93 of 432 procedures; 21.5%), and concurrent flap procedures (37 of 432 procedures; 8.6%).

The majority of implants (88.6%) were placed in submuscular location, using the mastectomy scar. The use of textured implants exceeded that of smooth implants (86.7% textured versus 13.3% smooth). The majority of implants (86.4%) were placed with pocket irrigation. The most common type of pocket irrigation used was antibiotic (60.9%) and betadine (53.7%).

Table 15: Surgical setting, anesthesia, and parenteral medication—Core Reconstruction

	Reconstruction N = 221 patients
Procedure Performed[1]	
• Immediate reconstruction	• 158 (71.5%)
• Delayed reconstruction	• 62 (28.1%)
• Contralateral augmentation	• 1 (0.5%)
Surgical Setting	
• Hospital	• 153 (69.2%)
• Surgical Center	• 68 (30.8%)
Type of Anesthesia	
• General (± Local)	• 219 (99.1%)
• Local Only	• 2 (0.9%)
Parenteral Medication[2]	
• Antibiotics	• 209 (94.6%)
• Steroid	• 52 (23.5%)
• Anesthetic	• 1 (0.5%)
• None	• 11 (5.0%)

Notes: [1]The majority of patients undergoing immediate reconstruction had tissue expanders (140 of 158 patients). The majority of patients undergoing delayed reconstruction had tissue expanders (53 of 62 patients). Contralateral augmentation refers to side opposite of tram flap reconstruction.
[2]The sum of parenteral medication exceeds 100% because more than one type of medication may have been used for an individual patient.

Table 16: Surgical Characteristics—Core Reconstruction

	Reconstruction N = 361 Implants
Incision Site	
• Mastectomy Scar	• 276 (76.5%)
• Inframammary	• 72 (19.9%)
• Periareolar	• 7 (1.9%)
• Breast Scar	• 4 (1.1%)
• Lateral	• 2 (0.6%)
Implant Location	
• Submuscular-Complete	• 109 (30.2%)
• Submuscular-Partial	• 211 (58.4%)
• Subtissue Flap	• 32 (8.9%)
• Subglandular	• 8 (2.2%)
• Subcutaneous	• 1 (0.3%)
Product Styles	
• Style 40 (Smooth, round)	
• Style 45 (Smooth, round)	• 43 (11.9%)
• Style 110 (Textured, round)	• 5 (1.4%)
• Style 120 (Textured, round)	• 64 (17.7%)
• Style 153 (Textured, contoured)	• 15 (4.2%)
	• 234 (64.8%)
Surgical Pocket Irrigation[1]	
• Antibiotic	• 220 (60.9%)
• Betadine	• 194 (53.7%)
• Local Anesthetic	• 93 (25.8%)
• Not Reported	• 3 (0.8%)
• None	• 49 (13.6%)

Notes: [1]The sum of pocket irrigation exceeds 100% because more than one type of pocket irrigation may have been used for an implant.

Note that of the 221 Core Reconstruction patients, all patients underwent breast implantation due to mastectomy with some patients also undergoing contralateral augmentation for symmetry. There were 15 patients who did not have breast cancer at the time of breast implantation but presumably were at high risk of developing breast cancer: 14 patients underwent bilateral prophylactic mastectomy, and 1 patient underwent unilateral prophylactic mastectomy.

C. Local Complications—Core Reconstruction Cohort

Table 17 below summarizes the 3 year cumulative Kaplan-Meier (KM) risk rates of first occurrence of complications occurring in ≥ 1% patients reported on a by-patient basis.

Table 17: By patient cumulative Kaplan-Meier (KM) risk rates of first occurrence (95% confidence interval) of local complications[1] occurring in ≥ 1%[2] at 3 years of follow-up—Core Reconstruction Cohort.

	Core Reconstruction N = 221 Patients	
Complication	Rate	(95% CI)
Asymmetry[1]	15.3%	(8.0%, 22.6%)
Breast Pain[1]	6.0%	(1.2%, 10.8%)
Bruising	4.1%	(0.0%, 8.2%)
Capsular Contracture III/IV	16.1%	(8.7%, 23.6%)
Delayed Wound Healing[1]	2.3%	(0.0%, 5.4%)
Implant Malposition[1]	5.2%	(0.8%, 9.7%)
Implant Rupture[3]	6.3%	(1.3%, 11.3%)
Infection	2.3%	(0.0%, 5.4%)
Lymphedema	1.0%	(0.0%, 3.0%)
Other Nipple Complication	9.3%	(3.3%, 15.2%)
Ptosis	1.4%	(0.0%, 3.8%)
Redness	6.4%	(1.3%, 11.4%)
Removal/Replacement	25.3%	(16.9%, 33.6%)
Reoperation	45.9%	(36.8%, 55.1%)
Scarring[4]	6.0%	(1.2%, 10.8%)
Seroma/Fluid Collection	5.1%	(0.6%, 9.5%)
Skin Rash	2.7%	(0.0%, 6.1%)
Swelling	16.4%	(9.1%, 23.8%)
Tissue/Skin Necrosis	6.1%	(1.1%, 11.1%)
Wrinkling/Rippling[1]	3.5%	(0.0%, 7.2%)

Notes: [1]Includes reports of only ≥ moderate severity for the complications of asymmetry, breast pain, capsule calcification, delayed wound healing, implant malposition, irritation/inflammation, loss of nipple sensation, nipple complications, palpability/visibility, skin sensation changes, and wrinkling.

[2]Capsule calcification (0%), hematoma (0.9%), extrusion (0.5%), palpability/visibility (0.5%), irritation (0%), lymphadenopathy (0.5%), nipple paresthesia/hypersensitivity/loss of nipple sensation (0%), pneumothorax (0.5%), and venous congestion (0.5%) not shown.

[3]Includes 8 implant ruptures confirmed via explant and 5 unconfirmed ruptures (3 of these are actually not ruptured: 1 by explant and 2 by re-review of MRI when considering implants are double lumen) for a total of 13 implant ruptures in 12 patients. (See Figure 2 for details on rupture.)

[4]Includes all scarring complications.

Reoperation:

With respect to **reoperation**, there were a total of 242 additional surgical procedures performed in 127 reoperations in 92 of the 221 patients (41.6%) through 3 years of follow-up in the Core Reconstruction Cohort. On a by-implant basis, 124 of the 361 primary implants (34.3%) underwent at least one reoperation. Of the 92 patients undergoing at least one reoperation, the majority (67 patients, 72.8%) underwent one reoperation; 18 patients (19.6%) underwent 2

reoperations, and 7 patients (7.6%) underwent 3 or more reoperations. Of the 127 reoperations, 78.8% involved one or two procedures per reoperation.

Table 18 summarizes the types of reoperation procedures performed through 3 years in the Core Reconstruction Cohort, with differences from the sponsor's categorization explained in the footnotes to the table. The two most commonly performed procedures were capsule related (22.3%) and removal with replacement (21.5%).

Table 18: Types of reoperation procedures performed through 3 years--Core Reconstruction Cohort.

Type of Procedure	Core Reconstruction N = 242 Procedures 3 Years
Removal with replacement	51 (21.1%)
Removal without replacement	5 (2.1%)
Capsulotomy	31 (12.8%)
Capsulorraphy	2 (0.8%)
Capsulectomy	21 (8.7%)
Scar revision/wound repair	47 (19.4%)
Implant reposition	13 (5.4%)
Biopsy/removal of tissue/lesion/cyst[1]	14 (5.8%)
Hematoma/seroma aspiration	9 (3.7%)
Unplanned nipple revision/tattoo	11 (4.5%)
Liposuction/Pocket Revision/Other[3]	38 (15.7%)

Notes: [1]Includes 3 of the sponsor's "other:" skin/subcutaneous tissue removal (2 procedures) and recontouring/reduction of axillary breast (1 procedure).
[2]Includes 13 pocket revision, 10 liposuction, 2 liposuction recontour, 3 mastopexy, 2 breast reduction, 2 flap procedure, 1 port-a-cath removal, 1 surgical exploration, 1 autogenous reconstruction, 1 reposition and tissue reconstruction, and 2 removal with unknown replacement.

Table 19 summarizes the primary reason for reoperation based on the suggested hierarchy described in section II.B. of this review. There were 46 of 127 primary reoperations for replacement/removal through 3 years; of these 46 reoperations, 44 were due to a complication—including unsatisfactory cosmetic result—and 2 were due to patient request. There were 16 primary capsule reoperations; all of these were due to a complication or unsatisfactory cosmetic result.

Table 19: Primary reason[1] for reoperation and primary procedure performed through 3 years—Core Reconstruction Cohort.

Primary Reason	Procedure	Reoperations N = 127
Device Rupture	Replacement/Removal	5 (3.9%)
	Exploration of Breast/Implant	1 (0.8%)
Capsular Contracture	Replacement/Removal	9 (7.1%)
	Capsule Procedure	6 (4.7%)
Extrusion	Replacement/Removal	1 (0.8%)
Necrosis	Wound Repair	1 (0.8%)
	Nipple Revision/Tattoo	1 (0.8%)
Healing Related	Wound Repair	6 (4.7%)
	Hematoma/Seroma Aspiration	6 (4.7%)
	Nipple Revision/Tattoo	4 (3.1%)
	Replacement/Removal	2 (1.6%)
	Capsule Procedure	1 (0.8%)
	Scar Revision	1 (0.8%)
	Excess Tissue/Cyst Removal	1 (0.8%)
Pain	Replacement/Removal	2 (1.6%)
Unsatisfactory Cosmetic Result	Scar Revision	25 (19.7%)
	Removal/Replacement	22 (17.3%)
	Capsule Procedure	9 (7.1%)
	Reposition Implant	6 (4.7%)
	Liposuction	3 (2.4%)
	Pocket Revision	2 (1.6%)
	Excess Tissue/Lesion Removal	2 (1.6%)
	Breast Reduction	1 (0.8%)
	Mastopexy	1 (0.8%)
Iatrogenic/Traumatic Injury	Replacement/Removal	1 (0.8%)
Breast Cancer	Replacement/Removal	2 (1.6%)
Patient Request	Removal/Replacement	2 (1.6%)
Other	Other	2 (1.6%)
	Nipple Revision/Tattoo	1 (0.8%)
	Excess Tissue/Lesion Removal	1 (0.8%)

Notes: [1]Heirarchy: device malfunction/rupture, infection, capsular contracture, extrusion, necrosis, healing related (hematoma/seroma, delayed wound healing), pain, unsatisfactory cosmetic result (contour deformity, malposition, wrinkling/rippling, palpability/visibility, asymmetry, ptosis, scarring), iatrogenic or traumatic injury, breast cancer, biopsy, patient request (style/size change, anxiety), other.

Implant Replacement/Removal:

With respect to **implant replacement/removal**, of the 361 primary reconstruction devices implanted, there were 56 implants removed (15.5%) through 3 years for any reason—**Table 20**—which were removed/replaced in 46 reoperations. Of the 56 implant removal/replacements, the majority (52; 92.9%) was removed/replaced to treat a complication, including those complications categorized as cosmetic, and 4 implants (7.1%) were removed/replaced due to patient request. Of the 221 Core Reconstruction patients, 46 patients (20.8%) underwent at least

one removal/replacement through 3 years, with 41 patients (51 implants) undergoing replacement, and 5 patients (5 implants) undergoing removal without replacement. Of the 51 implants replaced, 23 (45.1%) were for a decrease in size.

Table 20: Primary reason[1] for implant replacement/removal through 3 years—Core Reconstruction

Primary Reason	3 Years N = 56 Implants Removed
Complication Treatment/Cosmetic Outcome	52 (92.9%)
Rupture	5 (8.9%)
Capsular Contracture	12 (21.4%)
Extrusion	1 (1.8%)
Hematoma/Seroma	2 (3.6%)
Pain	2 (3.6%)
Contour Deformity	2 (3.6%)
Malposition	8 (14.3%)
Wrinkling	3 (5.4%)
Asymmetry	13 (23.2%)
Scarring	1 (1.8%)
Iatrogenic/Traumatic Injury	1 (1.8%)
Breast Cancer	2 (3.6%)
Patient Choice	4 (7.1%)
Change Size/Style	4 (7.1%)

Notes: [1]See section II.B. of this review, "Core Study Data Reporting" under "reoperation" for description of hierarchy.

Compliance of serial MRI screening:

Recall that a subset of Core Study patients underwent **serial MRI screening** for determination of asymptomatic (silent) rupture. For the Core Reconstruction cohort, 108 of the total 221 patients (170 of the total 361 devices) were enrolled in the serial MRI subset cohort screening for asymptomatic rupture. Of this 108 Core Reconstruction patient subset, 101 patients (93.5%) had their first serial MRI screening at approximately 1 year after implantation; 7 patients were lost to follow-up at this time point (6.5%). At the time of database closure there were no Core Reconstruction patients due for their second serial MRI screening at approximately 3 years after implantation. **In summary, there were 170 implants in 101 patients included in the MRI subset for Core Reconstruction. On a by-implant basis, this represents 47.1 % of the total 361 Core Reconstruction implants.** The findings of this MRI screening are detailed the "Rupture" section below.

Rupture:

The sponsor was asked to provide reports of all diagnostic studies related to implant rupture, and surgical operation notes of all explantations related to implant rupture. The following summary incorporates this information.

Of the 361 total Core Reconstruction implants, **15 implants were initially reported as "suspected" ruptured** through 3 years of follow-up: 2 implants reported via ultrasound, 3 implants with an unknown initial reason reported, 1 reported at explant, and 9 reported via the

MRI screening subset (described above) of 170 Core Reconstruction implants which underwent MRI screening for asymptomatic rupture at approximately 1 year following implantation. These "suspected" ruptures, in some cases, underwent additional evaluation, which is depicted in **Figure 2: Flowchart of Ruptures—Core Reconstruction** below. The following text in this section explains the sponsor's characterizations of these suspected ruptures as shown in **Figure 2.**

The 2 implants identified via ultrasound were in the same patient, who complained of asymmetry. Ultrasound examination indicated an ovoid hypoechoic region with implant contour folding of one implant and a normal exam of the other implant. At the time of explant of these 2 implants, one intracapsular rupture was noted, and 1 was reported as not ruptured. The implant noted as not ruptured at explant was not returned to the sponsor as part of the Device Retrieval Study. Note that this patient developed bradycardia and atrial fibrillation during the explant procedure, necessitating coumadin therapy, according to the explanting physician's notes.

Of the 3 implants reported as suspected of rupture with an unknown method reported, one was initially suspected by a flattening of the breast shape noted on physician exam 3 years after implantation. An MRI was obtained, indicating no evidence of rupture, and at subsequent explantation, no rupture was noted. This implant is classified as "unconfirmed" because the explant report was received after the data of database closure. This implant was not returned to the sponsor as part of the Device Retrieval Study. The other 2 suspected ruptures reported with an "unknown" method were actually from the MRI screening subset cohort and were noted to have evidence of rupture from the Local (but not the Central) radiologist. After informing the Local radiologist that these 2 implants were double (gel) lumen, a second reading of the MRI indicated no evidence of rupture (these are classified as "unconfirmed" by the sponsor because the second MRI reading was received after the March 27, 2003 cut off date for data closure).

For the 1 implant suspected ruptured through explant, it was an initial MRI as part of the MRI screening subset cohort which indicated evidence of rupture. Intracapsular rupture was noted at the time of explant. In Figure 2, this implant is included in the MRI group.

Of the **9 suspected implant ruptures reported by the sponsor as from MRI screening** (note that if the implant described above suspected at "explant" is included, there are actually 10 identified from MRI screening) all 9 were asymptomatic and were determined to have evidence of rupture by either the Local or Central MRI radiologist. Agreement between the Local and Central MRI radiologists was 90% for the Core Reconstruction cohort.

Of the 9 suspected MRI ruptures reported by the sponsor (Figure 2 includes the 1 explant in this group), 7 have undergone explantation and 2 have not undergone explantation. Of those undergoing explantation, at explant, 6 implants were reported as ruptured (all were intracapsular), and 1 implant was reported as not ruptured. This latter implant reported as not ruptured at explant was not returned to the sponsor as part of the Device Retrieval Study.

Of the 2 implants suspected of rupture via MRI but not having undergone explantation, 1 implant has undergone a second MRI approximately 1 year after the first, which also shows evidence of rupture. However, the physician has elected to defer explant and to follow the patient. For the

second of these implants, the physician has elected to defer explant and a second MRI is planned. These latter two implants are categorized as "unconfirmed" by the sponsor.

In summary, the rupture rate reported by the sponsor includes **13 ruptured implants through 3 years of follow-up in 12 patients: 8 confirmed via explant and 5 unconfirmed** (3 of these classified as "unconfirmed" have undergone additional follow-up with 1 implant reported as intact at explant, and 2 reported as intact following re-review of the MRI scans when considering that the implants are double lumen).

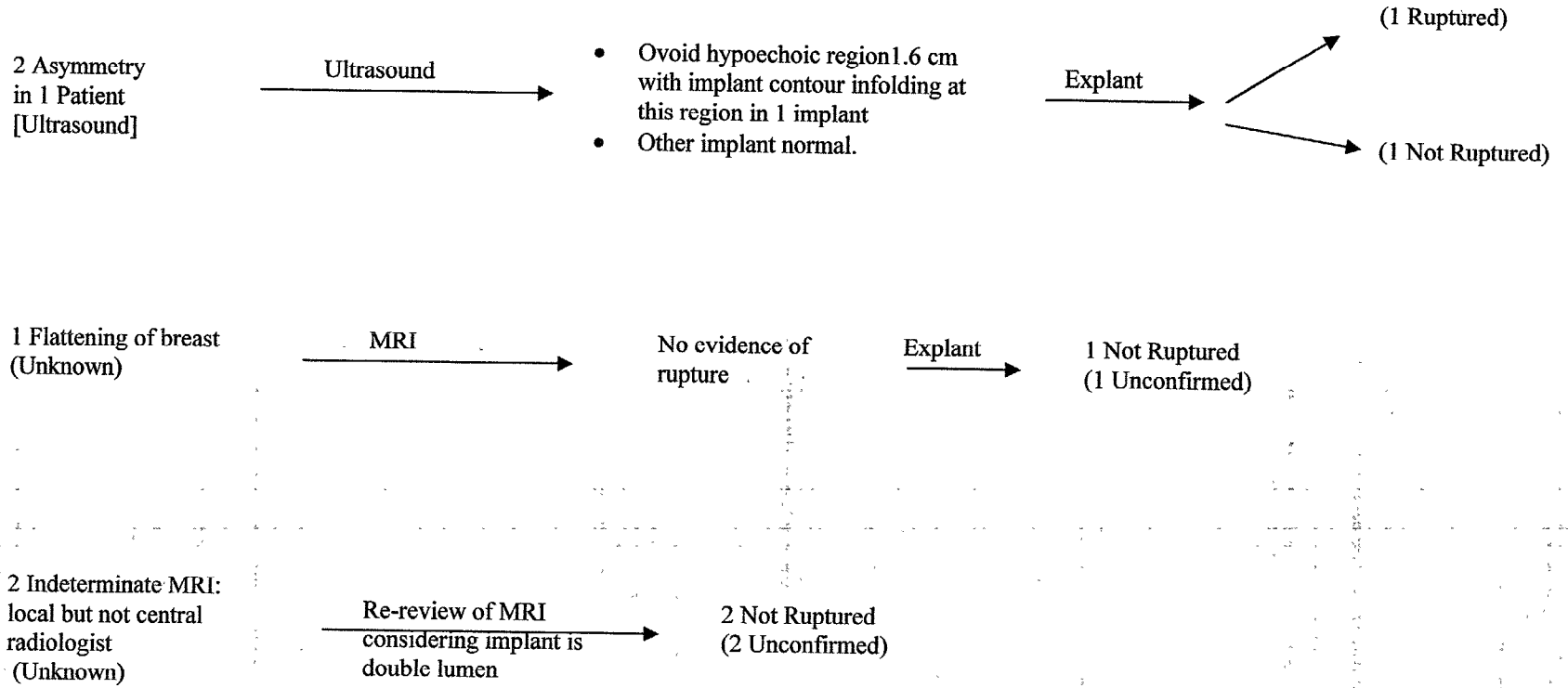
Of the 8 implant ruptures confirmed by explant, 6 were asymptomatic and found from MRI screening, according to the sponsor. If the 1 implant from the MRI subset but reported as suspected at "explant" is included, **then 7 of the 8 confirmed ruptures were asymptomatic and identified by MRI screening. Of the 13 total ruptures—including those classified as unconfirmed—8 were from MRI screening.**

The sponsor reports a 3 year by-implant cumulative Kaplan-Meier **silent rupture rate** of 4.7% (95% CI: 1.5%, 7.9%) based on 8 implant ruptures, highlighted in grey in Figure 2. The 3 year by-implant cumulative Kaplan-Meier **overall rupture rate** (including the 8 implants reported as "confirmed ruptured" and the 5 implants reported as "unconfirmed") is 4.2% (95% CI: 2.0%, 6.5%).

Recall that less than half of the implants in the Core Reconstruction cohort are included in the MRI screening subset and that only the first of 5 consecutive screenings have occurred. Had a larger proportion of patients undergone MRI screening, the rupture rate would likely be higher. Note that compared to the Core Augmentation and Core Revision MRI subsets which was approximately 30%, the Core Reconstruction MRI subset was larger (about 45%), with a larger contribution of asymptomatic ruptures to the rupture rate.

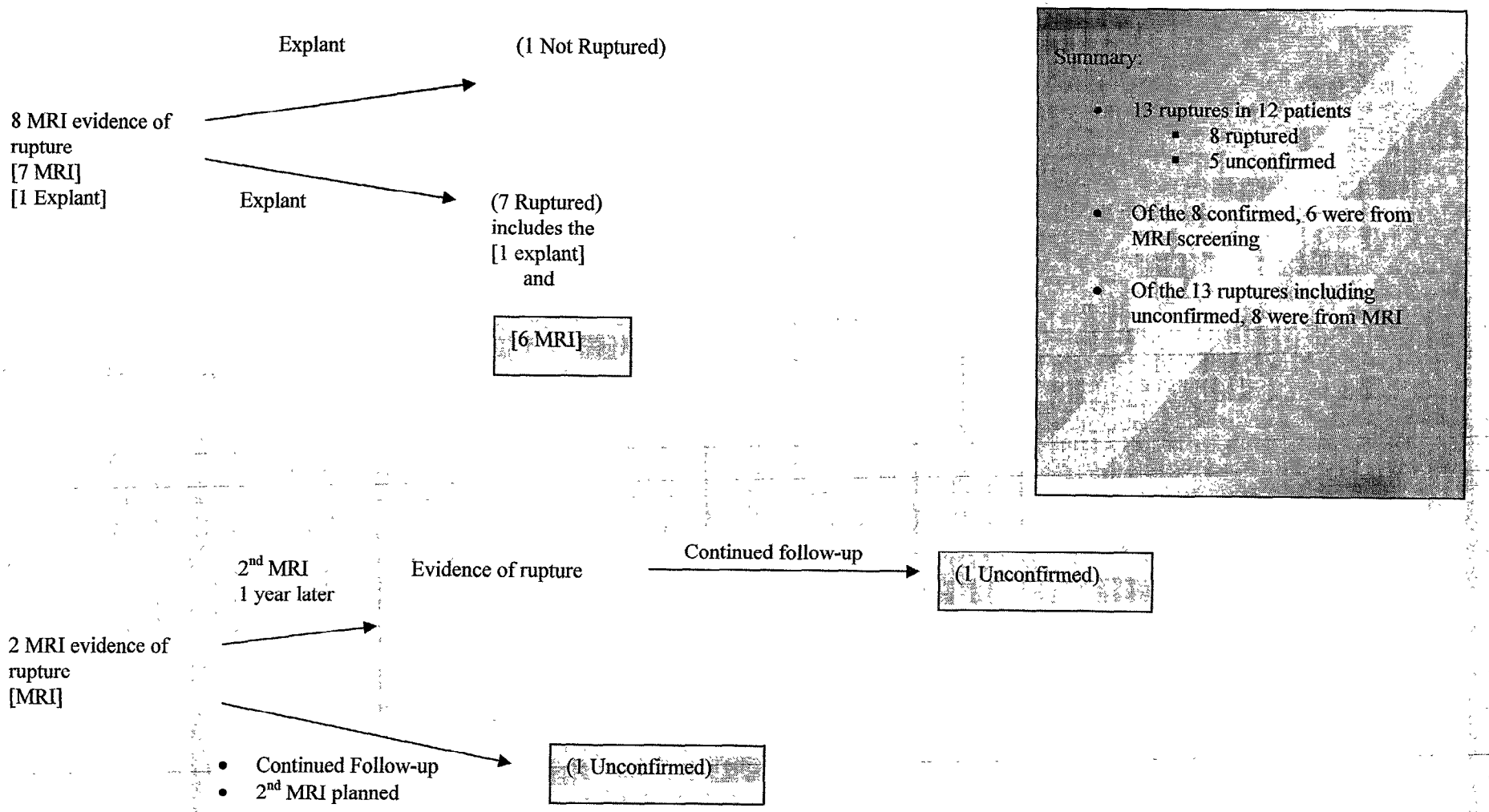
It is notable that 7 of the 8 confirmed ruptured implants in the Core Reconstruction Cohort were style 153, double lumen. In two cases, the ruptured double lumen implant was described as being in two segments upon explant. In some cases, visible tears were noted upon explant with free silicone gel found in the capsule in other cases. In some cases, when rupture was suspected on MRI, the films had to be re-read with the knowledge that the implants were double lumen, in which case a no rupture determination was subsequently made on MRI. Note that of the 2 implants reported as not ruptured at explant, and the 1 implant noted to be not ruptured at explant but classified as "unconfirmed", none were sent back to the sponsor for microscopic evaluation.

Figure 2: Flowchart of Rupture – Core Reconstruction Cohort



Notes: 1. Information in brackets indicates method of initial suspicion of rupture reported by the sponsor.
2. Information in parentheses indicates final rupture status reported by the sponsor. Shading of these represents implants included in determination of silent rupture rate.

Figure 2 (continued): Flowchart of Rupture – Core Reconstruction



Notes: 1. Information in brackets indicates method of initial suspicion of rupture reported by the sponsor.
2. Information in parentheses indicates final rupture status reported by the sponsor. Shading of these represents implants included in determination of silent rupture rate.

Complications following implant replacement:
Of the 41 patients (51 implants) who underwent implant removal with replacement, through 3 years, **complications following replacement** were reported in 12 patients (15 implants: capsular contracture (6 patients), asymmetry (3 patients), breast pain (2 patients), implant malposition (1 patient), and wrinkling/rippling (1 patient). Note that these values are not additive because an implant/patient may have reported more than one occurrence of a complication. Risk rates are not shown due to the small sample.

D. General Complications—Core Reconstruction Cohort

Before breast implantation, 51 of the 221 patients (23.1%) reported the following 62 **reproductive problems**: infertility (15 reports), spontaneous abortion (32 reports), planned abortion (7 reports), ectopic/molar pregnancy (3 reports), endometriosis (3 report), stillbirth (1 report), and uterine septum (1 report). Through 3 years after breast implantation, there were 2 patients (0.9%) reporting 2 reproductive problems: 1 report of no menses (this patient had also reported a spontaneous abortion pre-implant) and 1 report of planned abortion. Without information on the number of patients attempting reproduction (which was not collected in the Core Study) and without a comparison group of age-matched patients with similar co-morbidities (e.g. having breast cancer, chemotherapy, etc.) and followed for the same duration, it is not possible to draw definitive conclusions from these data; however, the percentage of patients reporting a problem post-implantation is lower than that pre-implantation. This could be due to less reproductive attempts or to reporting bias.

Before breast implantation, of the 116 patients who attempted to breast feed, 26 patients (22.4%) reported the following 32 **lactation problems**: inadequate milk production (14 reports), mastitis requiring treatment (7 reports), pain (6 reports), mastitis not requiring treatment (4 reports), and excess milk production (1 report). Through 3 years after breast implantation, of the 2 patients who attempted to breast feed, none reported lactation problems.

Prior to breast implantation, there were 218 of the 221 patients (98.6%) who reported **breast disease**, with 207 of these confirmed as malignant and 11 reported as benign. Recall that 206 of the Core Reconstruction patients had mastectomy for breast cancer, and 15 had prophylactic mastectomy. Through 3 years, there were 17 patient reports of post-implant breast disease: 5 confirmed malignant, 10 benign (i.e. fibrocystic disease, cyst, or other benign breast mass or lump), and 2 unconfirmed (1 patient had a cyst at her 3 year visit with pending follow-up and 1 patient had thickening with pending referral to her oncologist). Note that all 17 of the patients reporting post-implantation breast disease had a confirmed breast malignancy in either one or both breasts pre-implantation.

A summary of the 5 patients with **breast malignancy** following implantation is as follows: two patients had recurrence of the same tumor type in the same breast, one patient had metastasis of the original cancer into the lymph nodes, and two patients had a new malignancy in the contralateral breast but of the same tumor type.

Prior to implantation, 201 of the 221 patients had a pre-implant **mammogram**. The readings were normal or benign in 71 of these, and confirmed malignant in 130 patients. Through 3 years of follow-up, 108 of the 221 patients had a mammogram, of which 12 were reported abnormal through 3 years without such a report at baseline. Of the 12 abnormal mammogram results,

additional follow-up indicated that 1 had no breast disease, 3 had confirmed malignancy, 7 had benign breast disease, and 1 is pending follow-up of a breast cyst noted at her 3 year visit. Of the 3 patients with confirmed malignancy post-implant, 2 of these patients had pre-implant confirmed breast malignancy: one with recurrence in the same breast, and one with a new occurrence of malignancy in the non-implanted, contralateral breast.

With respect to **connective tissue/autoimmune disease (CTD)**, the sponsor reported one new post-implant report of CTD through 3 years of follow-up: a 42 year old patient with scleroderma 4 months following breast implantation. The sponsor was asked to provide the physician notes and laboratory tests pertaining to this diagnosis. Review of this information indicates a diagnosis of undifferentiated connective tissue disease (UCTD) manifested by arthritis, arthralgias, Raynaud's phenomenon, a history of gastritis and esophagitis with reflux disease diagnosed by upper endoscopy in the past, no evidence of skin thickening, a history of a positive ANA in the past with current ANA negative, and a slightly elevated RF of 38 IU/ml (normal <25 IU/ml). There is no mention of pulmonary or renal involvement. Based on this information, the diagnosis of UCTD is more likely than that of scleroderma in this patient.

Recall that the sponsor collected **CTD signs and symptoms** from the patients at baseline and at follow-up in the Activities and Lifestyle questionnaire to assist in determining CTD diagnoses, if present. This self-administered questionnaire includes a Modified Health Assessment Questionnaire (MHAQ), which assesses ability to perform various physical functions of daily living, and it includes a variety of signs and symptoms related to rheumatic diseases and to general health. Of the 221 Core Reconstruction patients, data are available for 161 patients (72.9%) for the MHAQ and for 162 patients (72.9%). These data are summarized in **Table 21** below. Recall that the intention of this questionnaire is to identify patients who warrant additional evaluation and referral to a rheumatologist. Without a control/comparison group of patients without implants followed for the same duration of follow-up and with similar demographic characteristics, conclusions cannot be made from these data.

Table 21: Summary of signs/symptoms categories and selected signs and symptoms reported through 2 years after implantation—Core Reconstruction.

Sign/Symptom Category	Pre-implant N = 162	Through 2 years post-implant N = 162
Skin[1]	20 (12.3%)	35 (21.6%)
Muscle[2]	56 (34.6%)	65 (40.1%)
Joint[3]	69 (42.6%)	94 (58.0%)
Neurological[4]	78 (48.1%)	97 (59.9%)
General[5]	56 (34.6%)	68 (42.0%)
Other[6]	37 (22.8%)	43 (26.5%)
Gastointestinal[7]	66 (40.7%)	73 (45.1%)
Urinary[8]	9 (5.6%)	9 (5.6%)
Joint Pain	17 (10.5%)	31 (19.1%)
Morning Stiffness	39 (10.1%)	70 (18.1%)

Notes: [1]Includes hair loss, skin rash, facial swelling, ecchymosis, purpura, unusual bruising, unusual bleeding, hives, other skin problem.
[2]Includes muscle weakness, muscle pain/aches/cramps, back pain, neck pain.
[3]Includes joint pain, swelling of hands, swelling of other joints, morning stiffness.
[4]Includes memory problems, problems with thinking, headaches, numbness/tingling of arms/legs, losing balance, ringing in ears.
[5]Includes fever, swollen glands, weight loss, weight gain, fatigue, generalized pain.
[6]Includes dry eyes, other eye problems, sores in mouth, dry mouth, problems with taste, trouble swallowing.
[7]Includes heartburn, stomach pain/cramps, nausea, vomiting, constipation, diarrhea, dark stool, blood in stool, loss of appetite, and moderate or greater gastrointestinal trouble.
[8]Includes urinating too often, problems with urination.

E. Additional Analyses of Safety Data—Core Reconstruction Cohort

The sponsor performed Cox proportional hazards regression analysis to determine whether the complications of reoperation, implant replacement/removal, implant rupture, capsular contracture, and infection were associated with patient age (≤40 years vs. >40 years), antibiotic pocket irrigation (yes vs. no), betadine pocket irrigation (yes vs. no), implant placement (submuscular vs. other), incision site (periareolar vs. inframammary vs. axillary vs. other), device texture (smooth vs. textured), and device shape (round vs. contoured), as suggested in FDA's Guidance document on Breast Implants. This information is based on an earlier date of database closure of August 30, 2002.

Findings are summarized in **Table 22** below. For the complications of reoperation, infection, and implant rupture, there were no associations. Round devices were 2.3 times more likely to undergo implant removal/replacement than contoured devices in the reconstruction cohort. Implants placed without betadine in the pocket were associated with a higher risk of capsular contracture, and implants placed in a non-submuscular position were also associated with a higher capsular contracture rate.

Table 22: Summary of risk factor analysis—Core Reconstruction Cohort

Complication Risk	Factor	Adjusted Risk Ratio (95% CI)
Capsular Contracture	No betadine pocket irrigation vs. yes	6.8 (2.7, 17.6)
Capsular Contracture	Other vs. submuscular placement	5.4 (1.9, 14.7)

F. Effectiveness—Core Reconstruction Cohort

The sponsor did not collect **breast size** information for the reconstruction patients.

The sponsor collected both patient and physician satisfaction. Because the patient satisfaction is more relevant, I will omit the summary of physician satisfaction information. The sponsor collected both **general patient satisfaction** and satisfaction based on pre-operative expectation. With respect to general patient satisfaction, of the 177 patients (of 221) who completed this questionnaire at 2 years, there was a small decline in mean satisfaction from the 0-4 week follow-up timepoint of 4.8 (SD 0.6) to 4.5 (SD 0.9) at 2 years. With respect to **patient satisfaction compared to pre-operative expectation** of satisfaction, of the 166 patients (of 221) who responded to these patient satisfaction questions, the majority of patients reported being satisfied or very satisfied with their implants at both 1 and 2 years post-implant. Approximately 9.0% of these patients reported being dissatisfied or very dissatisfied, and another 6.0% were neutral regarding their satisfaction at 2 years compared to their pre-operative expectations. There were small but statistically significant declines in patient satisfaction at both 1 and 2 years compared to their pre-operative expectations of satisfaction. The mean pre-operative expectation value of 4.6 (SD 0.5) was compared to 4.2 (SD 1.0) at 2 years.

With respect to the **Health Status Questionnaire (SF-36 and MOS-20),** the core reconstruction cohort reported statistically significant higher levels at baseline compared to normative values for most subscales of the SF-36: general health, social functioning, physical functioning, vitality, and mental health. At 2 years all subscales were generally higher than at baseline for the breast reconstruction cohort, with statistically significant improvement noted in role limitations due to physical health problems. The 2 year scores for the breast reconstruction cohort are numerically higher than the normative values, although statistical comparisons were not made. **Table 23** summarizes the results of selected health status measures. Note that most of the changes, even those that are worse, are small.

Table 23: Summary of selected health status/QOL measures—Core Reconstruction Cohort.

Assessment method	Statistically significant change in pre- to 2 year post-implant score	Direction of change
SF-36 Role Emotional	No	Better
SF-36 Role Physical	Yes	Better
SF-36 General Health	No	Worse
SF-36 Pain	No	Better
SF-36 Social	No	Better
SF-36 Vitality	No	Better
SF-36 Physical	No	Better
SF-36 Mental Health	No	Better
MOS-20 Health Perceptions	No	Worse
MOS-20 Physical Functioning	Yes	Better
MOS-20 Social Functioning	No	Better
MOS-20 Mental Health	No	Better
TSCS Physical Self	No	Worse
Rosenberg Self Esteem	No	Worse
Semantic Differential	No	Better
Body Esteem-Total Score	No	Worse
Body Esteem-Sexual Attractiveness	No	Better
Body Esteem-Weight Concern	No	Worse
Body Esteem-Physical Condition	No	Worse

V. CORE STUDY RESULTS—REVISION COHORT

A. Patient Disposition—Core Revision Cohort

Enrollment of the revision cohort occurred between January of 1999 and June of 2000 by 22 investigators at 27 sites. Investigators enrolled as few as 1 and as many as 20 patients. Most investigators utilized one or two of the 7 styles for which the sponsor is seeking approval. Note that styles 10 and 20 were not utilized in this cohort (and were not used in the Core Augmentation or Core Reconstruction cohorts).

A total of **225 patients (432 implants) were enrolled** and implanted. As of the March 27, 2003 data cut off date, 91.1% of the Core Revision patients were eligible for a 3 year (+ 2 months) visit. Through 3 years (up to 42 months), there were 16 patients who were known to have discontinued from the study: 4 due to death (1 due to ovarian cancer, 1 due to cervical cancer, 1 due to metastatic breast cancer, and one due to unknown causes); 2 due to patient choice (one due to dissatisfaction with scars and one due to travel); and 10 due to removal without replacement of all study implants.

Of the 10 patients who underwent removal without replacement of all study implants (19 implants) through 3 years, 2 patients had their implants replaced with saline-filled implants, 1 patient had unresolved capsular contracture, 3 patients had another manufacturer's implants or a non-study gel-filled implant, and in 4 patients an unknown reason was given for not replacing with study implants. Five of these patients reported several complications and 5 reported no

complications. Using the hierarchy for implant removal, the primary reason for implant removal in these patients is as follows: capsular contracture/firmness (2 patients), seroma (1 patient), swelling (1 patient), and pain (1 patient). Note that the sponsor included these complications in the determination of KM risk rates.

Table 24 summarizes the patient disposition through 3 years. The **follow-up rate** through 3 years (actual divided by expected) is 83.8%. Through 2 years, the follow-up rate of 87.0%, which is not shown, is acceptable. Note that the sponsor used a +2 month window for determining those patients theoretically due; yet, they used a +6 month window for reporting cumulative deaths and explants. Because it is important to include all known reported deaths and explants in the reporting of patient disposition, **Table 24** below includes data with these inconsistent timepoints, and an explanation in the footnotes.

Table 24: Patient disposition through 3 years on a by-patient basis—Core Revision Cohort.

N = 225 patients enrolled N = 432 implants enrolled	
Theoretical follow-up[1]: N = 205 Expected follow-up[2]: N = 191 Actual follow-up: N = 160 (83.8%)	
Withdrawals N = 45	
Reason for withdrawal	Number of patients withdrawn
Death[3]	4
Implant removal[3,4]	10
Lost to follow-up[5]	31

Notes: [1]Based on follow-up to 38 months due to an additional 2 month window for the 3 year follow-up visit to determine theoretically due.
[2]Expected follow-up is theoretical follow-up minus deaths and removals without replacement.
[3]Based on follow-up to 42 months due to an additional 6 month window for determination of deaths and removals.
[4]Defined as removal without replacement of all study implants: 2 patients had their implants replaced with saline-filled implants, 1 patient had unresolved capsular contracture, 3 patients had another manufacturer's implants or a non-study gel-filled implant, and in 4 patients an unknown reason was given for not replacing with study implants. Five of these patients reported several complications; 5 of these reported no complications.
[5]Two of these were due to patient choice: one due to refusal to travel and one due to dissatisfaction with scar.

B. Demographics/Baseline Characteristics—Core Revision Cohort

The demographic and baseline characteristics are summarized in **Table 25** below. The median age of 44 years (range 18 to 80 years), is between that of the core augmentation cohort (34 years) and the core reconstruction cohort age (50 years).

Table 25: Patient demographic and baseline characteristics—Core Revision Cohort

	Revision N = 225 patients
Median age (range) in years	44 (18 – 80)
Number (%) Caucasian	197 (87.6%)
Median weight (range) in pounds	125 (92-220)

The surgical setting, type of anesthesia used, distribution of implant styles used, incision site, implant location, and intraoperative medication use is summarized in **Tables 26 and 27**. Most patients had revision of a previous augmentation, had general anesthesia, and had parenteral medication consisting mostly of antibiotics. There were 2 reports of intraoperative complications: one case of "calcified shell and ruptured original implant" and one case of "calcified shell and silicone slick fragile implant." Use of perioperative drains occurred in less than half of the 432 implant procedures (43.5%). Of the 348 (of 432) implants placed with a concurrent procedure (an implant may have been placed with more than one concurrent procedure), the majority of procedures consisted of capsule procedures (339 of 348 implants; 97.4%%), followed by mastopexy (57 of 348 implants; 16.4%), and mastectomy/flap procedures (20 of 348 implants; 5.7%), nipple procedures (18 of 348 implants; 5.2%), scar/pocket revision (18 of 348 implants; 5.2%), and biopsy/fat injection/tissue expander removal (7 of 348 implants; 2.0%).

The majority of implants (251 of 432 implants; 58.1%) were placed via an inframammary incision site, and 278 (64.4%) implants were placed in a submuscular location. The use of textured implants exceeded that of smooth implants (61.1% textured; 38.9% smooth). The majority of implants (91.1%) were placed with pocket irrigation, and the most common type of pocket irrigation was antibiotic (70.1% of implants) followed by betadine (38.2% of implants).

Table 26: Surgical setting, anesthesia, and parenteral medication—Core Revision

	Revision N = 225 patients
Initial Indication	
• Previous augmentation	• 171 (76.0%)
• Previous reconstruction	• 54 (24.0%)
Surgical Setting	
• Doctor's Office	• 80 (35.6%)
• Surgical Center	• 73 (32.4%)
• Hospital	• 72 (32.0%)
Anesthesia	
• General (± Local)	• 182 (80.9%)
• Local Only	• 43 (19.1%)
Parenteral Medication[1]	
• Antibiotics	• 198 (88.0%)
• Steroid	• 58 (25.8%)
• Anesthetic/Sedative	• 19 (8.4%)
• None	• 26 (11.6%)

Notes: [1]The sum of parenteral medication exceeds 100% because more than one type of medication may have been used for an individual patient.

Table 27: Surgical characteristics—Core Revision

	Revision N = 432 implants
Incision Site	
• Inframammary	• 251 (58.1%)
• Periareolar	• 102 (23.6%)
• Mastectomy/Breast Scar	• 67 (15.5%)
• Axillary/Lateral	• 6 (1.4%)
• Mastopexy Incision	• 6 (1.4%)
Implant Location	
• Submuscular-Partial	• 226 (52.3%)
• Submuscular-Complete	• 52 (12.0%)
• Subglandular	• 133 (30.8%)
• Subcutaneous	• 12 (2.8%)
• Subtissue Flap	• 9 (2.1%)
Product Styles	
• Style 40 (Smooth, round)	• 136 (31.5%)
• Style 45 (Smooth, round)	• 32 (7.4%)
• Style 110 (Textured, round)	• 104 (24.1%)
• Style 120 (Textured, round)	• 35 (8.1%)
• Style 153 (Textured, contoured)	• 125 (28.9%)
Surgical Pocket irrigation[1]	
• Antibiotic	• 303 (70.1%)
• Betadine	• 165 (38.2%)
• Local Anesthetic	• 126 (29.2%)
• None	• 39 (9.0%)

Notes: [1]The sum of pocket irrigation exceeds 100% because more than one type of pocket irrigation may have been used for an implant.

The **reason for revision** on a by-patient and by-reason basis is summarized in **Table 28**. There may have been more than one reason for revision reported for an individual patient. The most common reason for revision on both a by-patient and by-reason basis is for capsular contracture or pain, followed by a request to change breast size and suspected rupture/deflation/patient concern.

Table 28: Reason for revision—Core Revision Cohort

Reason for Revision	N	% Revision N = 387 Reasons	% Revision N = 225 Patients[1]
Capsular Contracture/Pain	131	33.9%	58.2%
Change Size[2]	55	14.2%	24.4%
Suspected rupture/deflation/patient concern[3]	54	14.0%	24.0%
Rippling	46	11.9%	20.4%
Asymmetry	40	10.3%	17.8%
Malposition	31	8.0%	13.8%
Palpability/Ptosis[4]	17	4.4%	7.6%
Breast Cancer/Fibrocystic Disease[5]	9	2.3%	4.0%
Infection	2	0.5%	0.9%
Necrosis/deformity	2	0.5%	0.9%

Notes: [1]The sum of % patients exceeds 100% because more than one reason may have been reported for an individual patient.

[2]Thirty-eight of these were to increase size, 16 were to decrease size, and 1 was reported as unknown change in size.

[3]Forty-two of these were for suspected rupture, 11 for suspected deflation, and 1 for patient concern.

[4]Sixteen of these were for ptosis, and 1 was for palpability.

[5]Eight of these were for breast cancer and 1 for fibrocystic disease.

C. Local Complications—Core Revision Cohort

Table 29 below summarizes the 3 year cumulative KM risk rate of first occurrence of local complications occurring in ≥1% of patients reported on a by-patient basis.

Table 29: By patient cumulative Kaplan-Meier (KM) risk rates of first occurrence (95% confidence interval) of local complications[1] occurring in ≥ 1%[2] at 3 years of follow-up—Core Revision Cohort..

	Core Revision N = 225 Patients	
Complication	Rate	(95% CI)
Asymmetry[1]	5.1%	(2.0%, 8.2%)
Breast Pain[1]	7.2%	(3.7%, 10.8%)
Bruising	4.3%	(1.5%, 7.0%)
Capsular Contracture III/IV	9.8%	(5.7%, 13.9%)
Hematoma	2.7%	(0.6%, 4.9%)
Implant Malposition[1]	4.9%	(1.9%, 7.8%)
Implant Rupture[3]	3.6%	(1.0%, 6.3%)
Infection	2.8%	(0.6%, 4.9%)
Irritation[1]	1.0%	(0.0%, 2.3%)
Other Nipple Complication	2.9%	(0.6%, 5.3%)
Palpability/Visibility	2.0%	(0.0%, 3.9%)
Ptosis	2.0%	(0.1%, 3.9%)
Redness	5.8%	(2.6%, 9.0%)
Removal/Replacement	13.4%	(8.7%, 18.1%)
Reoperation	33.4%	(26.9%, 39.8%)
Scarring[4]	8.6%	(4.7%, 12.5%)
Seroma/Fluid Collection	7.1%	(3.6%, 10.5%)
Skin Rash	2.4%	(0.3%, 4.4%)
Swelling	15.9%	(11.0%, 20.8%)
Tissue/Skin Necrosis	2.3%	(0.3%, 4.4%)
Wrinkling/Rippling[1]	5.0%	(2.0%, 8.0%)

Notes: [1]Includes reports of only ≥ moderate severity for the complications of asymmetry, breast pain, capsule calcification, delayed wound healing, implant malposition, irritation/inflammation, loss of nipple sensation, nipple complications, palpability/visibility, skin sensation changes, and wrinkling.
[2]Capsule calcification (0%), delayed wound healing (0.9%), extrusion (0.5%), lymphadenopathy, (0%), lymphedema (0%), loss of nipple sensation (0%), nipple hypersensitivity/paresthesia (0%), pneumothorax (0%), skin sensation changes (0.5%), and other (0.4%) not shown.
[3]Includes confirmed rupture via explant of 5 implants and 3 suspected but unconfirmed implant ruptures for a total of 8 implant ruptures in 7 patients. Includes only clinically identified ruptures and not necessarily microscopically identified ruptures, unless noted clinically.
[4]Includes all scarring complications.

Reoperation:
With respect to **reoperation** there were a total of 190 additional surgical procedures performed in 100 reoperations in 70 of the 225 patients (31.1%) over the 3 years of follow-up in the Core Revision Cohort. On a by-implant basis, 107 of the 432 primary implants enrolled (24.8%) underwent at least one reoperation. Of the 70 patients undergoing at least one reoperation, the

majority (51 patients) underwent 1 reoperation; 11 patients underwent 2 reoperations, and 8 patients underwent ≥ 3 reoperations. Of the 100 reoperations, 78 involved 1 or 2 procedures. **Table 30 below summarizes the types of reoperation procedures** performed through 3 years in the Core Revision Cohort. The three most commonly performed procedures were capsule related (27.9%), implant removal with replacement (21.6%), and mastopexy (13.7%).

Table 30: Types of reoperation procedures performed through 3 years in the Core Revision Cohort.

	Core Revision N = 190 Procedures 3 Years
Removal with replacement	41 (21.6%)
Removal without replacement	5 (2.6%)
Capsulotomy	30 (15.8%)
Capsulorraphy	9 (4.7%)
Capsulectomy	14 (7.4%)
Mastopexy	26 (13.7%)
Scar revision/wound repair	18 (9.5%)
Implant reposition	7 (3.7%)
Biopsy/removal of tissue/lesion/cyst[1]	9 (4.7%)
Pocket revision/exploration of breast area or implant/suture removal	11 (5.8%)
Hematoma/seroma aspiration	10 (5.3%)
Unplanned nipple revision/tattoo	10 (5.3%)

Notes: [1]Includes one case of breast reduction

Table 31 summarizes the primary reason for reoperation based on the hierarchy summarized in section II.B. of this review. There were 29 of 100 reoperations for implant removal/replacement; of these 29 reoperations, 14 were due to a complication, 8 were due to an unsatisfactory cosmetic result, and 7 were due to patient choice. There were 20 capsule reoperations: of these, 12 were due to a complication and 8 were due to an unsatisfactory cosmetic result or other.

Table 31: Primary reason[1] for reoperation and primary procedure performed through 3 years—Core Revision Cohort.

Primary Reason	Procedure	Reoperations N = 100
Device Rupture	Replacement/Removal	5 (5.0%)
Infection	Replacement/Removal	1 (1.0%)
Capsular Contracture	Replacement/Removal	7 (7.0%)
	Capsule Procedure	9 (9.0%)
Extrusion	Pocket Revision	3 (3.0%)
Healing Related	Hematoma/Seroma Aspiration	8 (8.0%)
	Nipple Revision/Tattoo	7 (7.0%)
	Scar Revision/Wound Repair	4 (4.0%)
	Tissue/Skin Removal/Other	3 (3.0%)
	Capsule Procedure	2 (2.0%)
Pain	Replacement/Removal	1 (1.0%)
Unsatisfactory Cosmetic Result	Scar Revision	9 (9.0%)
	Removal/Replacement	8 (8.0%)
	Mastopexy	8 (8.0%)
	Capsule Procedure	7 (7.0%)
	Reposition Implant	3 (3.0%)
	Pocket Revision	3 (3.0%)
	Breast Reduction	1 (1.0%)
Iatrogenic/Traumatic Injury	Capsule Procedure	1 (1.0%)
Breast Cancer	Biopsy	1 (1.0%)
Biopsy	Biopsy	1 (1.0%)
Patient Request	Removal/Replacement	7 (7.0%)
Other	Capsule Procedure	1 (1.0%)

Notes: [1]Heirarchy: device malfunction/rupture, infection, capsular contracture, extrusion, necrosis, healing related (hematoma/seroma, delayed wound healing), pain, unsatisfactory cosmetic result (contour deformity, malposition, wrinkling/rippling, palpability/visibility, asymmetry, ptosis, scarring), iatrogenic or traumatic injury, breast cancer, biopsy, patient request (style/size change, anxiety), other.

Implant Replacement/Removal:

With respect to **implant replacement/removal,** of the 432 primary revision devices implanted, there were 46 implants removed (10.6%) through 3 years for any reason (**Table 32**), which were removed/replaced in 29 reoperations. Of the 46 implant removals, the majority (33 implants; 71.7%) were removed/replaced to treat a complication, including cosmetic complications, and 13 implants (28.3%) were removed/replaced due to patient request. Of the 46 implants removed/replaced, 41 were replaced and 5 were not replaced. Of the 225 Core Revision patients, 27 patients (12.0%) underwent at least one implant replacement/removal through 3 years, with 24 of these patients undergoing replacement and 3 patients not undergoing replacement.

Table 32: Primary reason[1] for implant replacement/removal through 3 years—Core Revision Cohort.

Primary Reason	3 Years N = 46 Implants Removed
Complication Treatment/Cosmetic Outcome	33 (71.7%)
Implant Rupture	6 (13.0%)
Infection	1 (2.2%)
Capsular Contracture	7 (15.2%)
Delayed Wound Healing	1 (2.2%)
Pain	1 (2.2%)
Malposition	8 (17.4%)
Asymmetry	1 (2.2%)
Ptosis	6 (13.0%)
Scarring	2 (4.4%)
Patient Choice for Style/Size Change	13 (28.3%)

Notes: [1]See section II.B. of this review, "Core Study Data Reporting" under "reoperation" for description of hierarchy.

Compliance of serial MRI screening:

Recall that a subset of Core Study patients underwent **serial MRI screening** for determination of asymptomatic (silent) rupture. For the Core Revision cohort, 77 of the total 225 patients (138 of the total 432 devices) were enrolled in the serial MRI subset cohort screening for asymptomatic rupture. Of this 77 Core Revision patient subset, 72 patients (93.5%) had their first serial MRI screening at approximately 1 year after implantation; 5 patients were lost to follow-up at this 1 year time point (6.5%). At the time of database closure there are no Core Revision patients due for their second serial MRI screening at approximately 3 years after implantation. **In summary, there were 138 implants in 72 patients included in the MRI subset for Core Revision. On a by-implant basis, this represents 32.0 % of the total 432 Core Revision implants.** The findings of this MRI screening are detailed in the "Rupture" section below.

Rupture:

The sponsor was asked to provide reports of all diagnostic studies related to implant rupture, and surgical operation notes of all explantations related to implant rupture. The following summary incorporates this information.

Of the 432 total Core Revision implants, **12 implants were initially reported as "suspected" ruptured** through 3 years of follow-up: 2 reported at explant/revision, 1 reported after ultrasound, 1 reported at reoperation, 4 reported following physician exam (reported symptoms were implant distortion, softer breast texture, decreased breast size, and pain/tenderness), and 4 reported via the **MRI screening subset** (described above) of 138 Core Revision implants which underwent MRI screening for asymptomatic rupture at 1 year following implantation. These "suspected" ruptures, in some cases, underwent additional evaluation, which is depicted in **Figure 3: Flowchart of Rupture—Core Revision** below. The following text in this section explains the sponsor's characterizations of these suspected ruptures as shown in **Figure 3**.

The two implants reported as suspected ruptured at explant were in the same patient. This patient noted nodules in one breast and a bulge in the other breast. An ultrasound evaluation was performed which showed extracapsular free silicone in the breast with nodules and an intact implant in the breast with a bulge. The patient underwent explantation by another physician, and the explant report is pending; the sponsor classifies these as "unconfirmed." These implants have not been returned to the sponsor as part of the Device Retrieval Study.

For the 1 implant reported as suspected ruptured via ultrasound, the patient had complained of itchiness of the breast prior to the ultrasound. At explant, the implant was reported as not ruptured. This implant was returned to the sponsor for microscopic evaluation as part of the Device Retrieval Study and found to be "intact and functional."

For the 1 implant reported as suspicious for rupture at reoperation, the patient had been involved in a motor vehicle accident and had trauma to the right breast with a normal physical examination. An MRI was obtained which showed evidence of rupture, and at explant, an intracapsular rupture was noted.

Of the 4 implants reported as suspected ruptured via physician exam, two were due to patients complaining of softer feel of the implant. In one case, physician examination indicated no implant palpable in the pocket, and at explant, rupture was noted. In the other case, an MRI was obtained which was read as indeterminate, and at subsequent explant, the implant was reported as not ruptured; this implant was not returned to the sponsor as part of the Device Retrieval Study. Another case of physician exam was due to a patient complaining of pain, palpability, wrinkling, and malposition. An ultrasound was suspicious for rupture, but a subsequent MRI indicated no rupture. The sponsor reports this as not ruptured. For the last suspected rupture identified by physician exam, the patient complained of implant rippling and a change in size. An MRI was obtained which indicated no rupture, and the sponsor reports this implant as not ruptured. To summarize the 4 implants suspected ruptured by physician exam, 2 underwent explantation (with one of these reported as ruptured and one of these reported as not ruptured) and the other two had MRI indicating no rupture for a total of 1 implant reported as ruptured and 3 implants reported as not ruptured.

Of the **4 suspected implant ruptures identified from MRI screening**, all were asymptomatic and all were determined as having some evidence of rupture. Agreement between the Central and Local MRI radiologist was 98.6%. Follow-up evaluation of these 4 suspected MRI ruptures is as follows: 3 implants were explanted and confirmed to have intracapsular rupture. The physician for the remaining one implant does not believe the implant has ruptured and has elected to continue to follow the patient. The MRI report in this case was read as having folds in the envelope but no frank rupture by the Local radiologist. The sponsor classifies this implant as "unconfirmed."

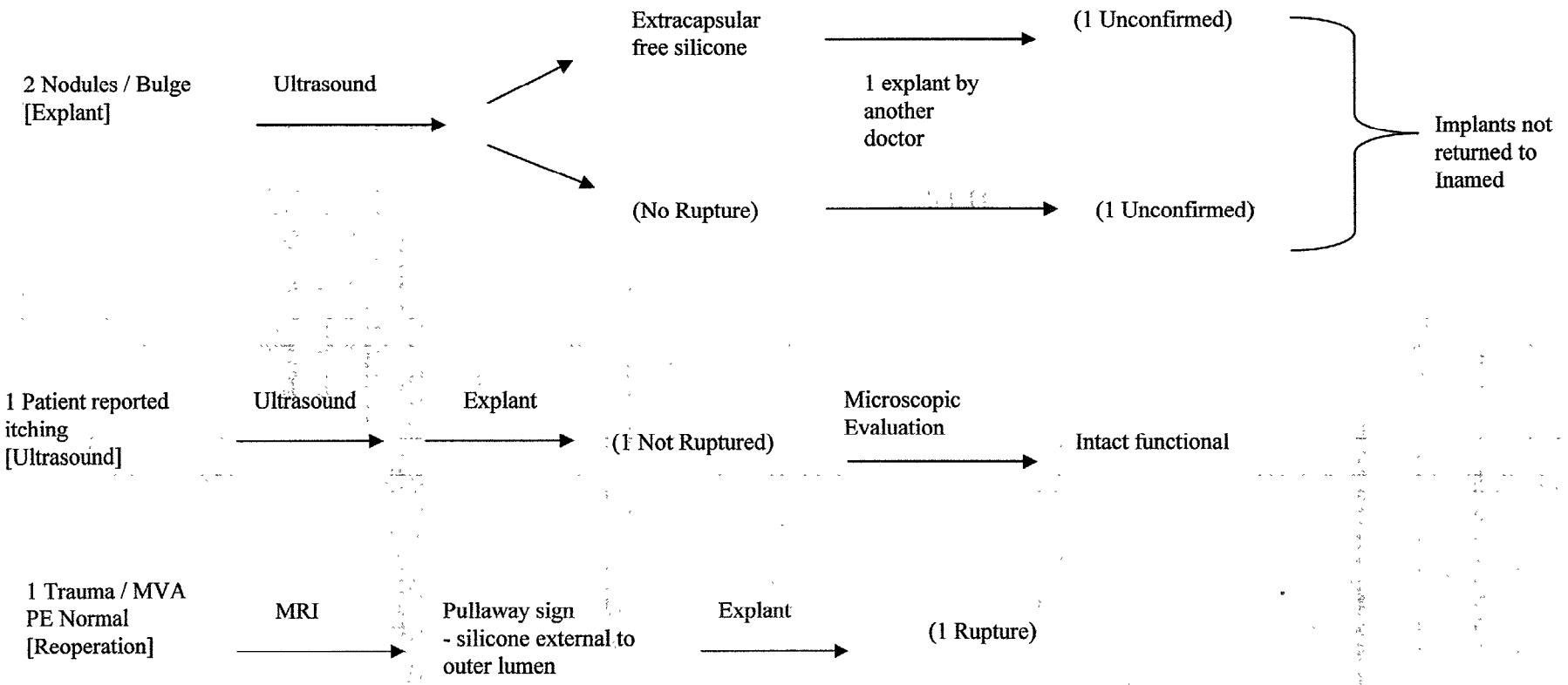
In summary, the rupture rate reported by the sponsor includes **8 ruptured implants in 7 patients through 3 years of follow-up: 5 confirmed via explant and 3 reported as unconfirmed. Of the 5 confirmed implant ruptures, 3 were asymptomatic and from the MRI screening subset; of the 8 total reported ruptures—including those categorized as unconfirmed—4 were from the MRI screening subset. Of the 9 total implants which were explanted due to**

suspicion for rupture, 5 were reported as ruptured and of these 5 ruptured implants, 3 were asymptomatic and were identified in the MRI screening subset.

The sponsor reports a 3 year by-implant cumulative Kaplan-Meier **silent rupture rate** of 2.9% (95% CI: 0.1%, 5.7%) based on 4 implant ruptures, highlighted in grey in Figure 3. The 3 year by-implant cumulative Kaplan-Meier **overall rupture rate** (including the 5 implants reported as "confirmed ruptured" and the 3 implants reported as "unconfirmed") is 2.2% (95% CI: 0.7%, 3.7%).

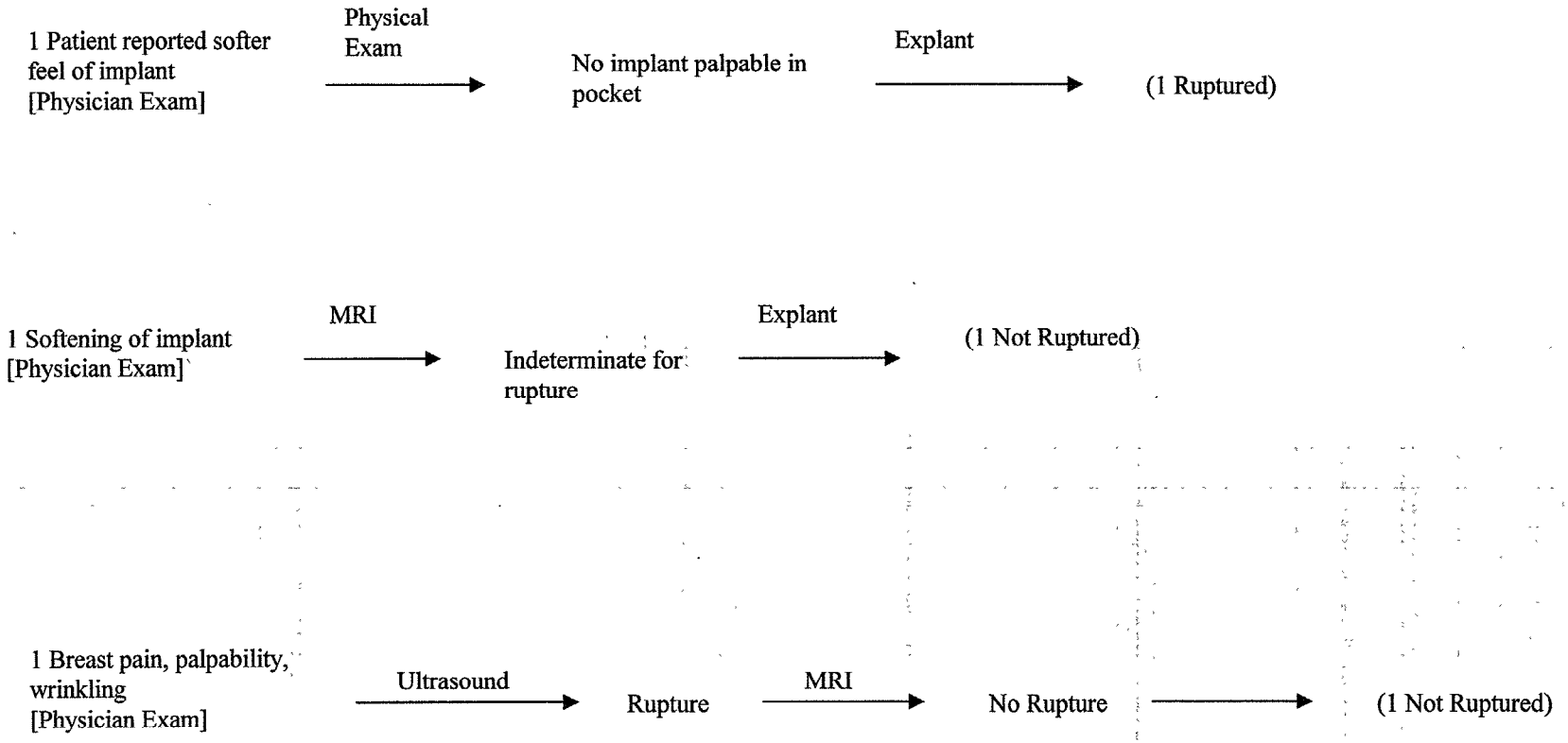
Recall that the MRI screening subset consisted of approximately one-third of the total Core Revision patients and included only the first of 5 serial MRI screenings. Had there been a greater proportion of patients screened, the rupture rate would likely be higher.

Figure 3: Flowchart of Rupture – Core Revision Cohort



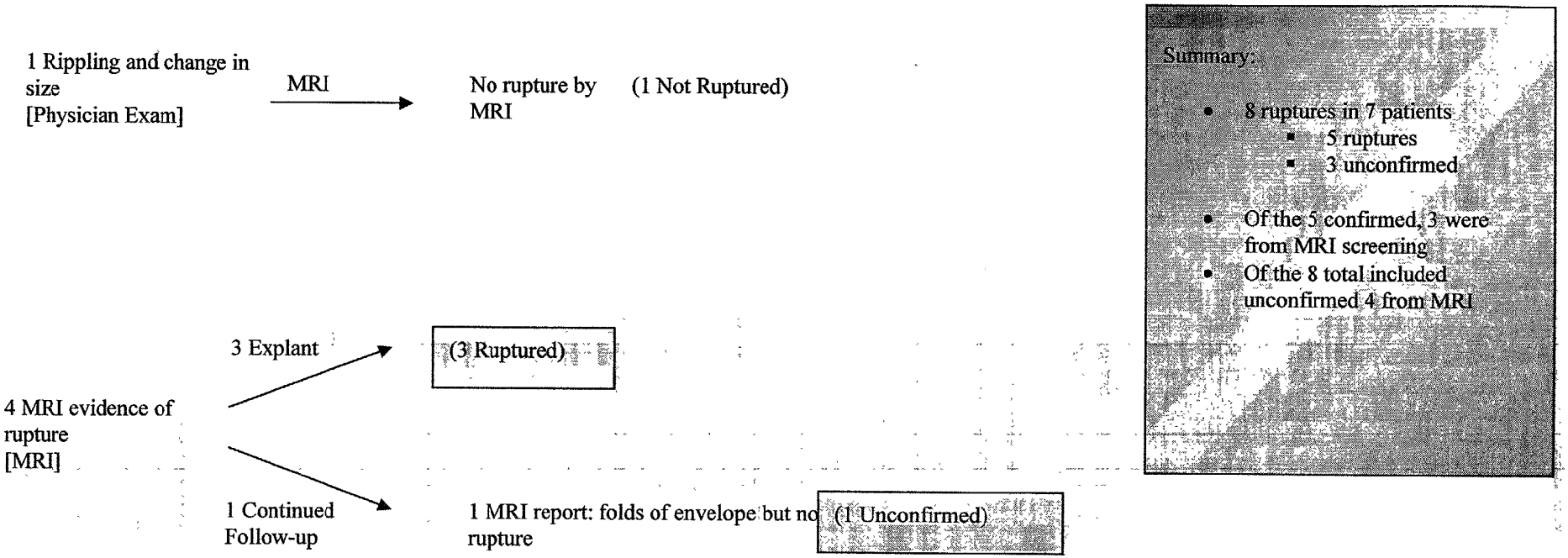
Notes: 1. Information in brackets indicates method of initial suspicion of rupture reported by the sponsor.
2. Information in parentheses indicates final rupture status reported by the sponsor. Shading of these represents implants included in determination of silent rupture rate.

Figure 3 (continued): Flowchart of Rupture – Core Revision Cohort



Notes: 1. Information in brackets indicates method of initial suspicion of rupture reported by the sponsor.
2. Information in parentheses indicates final rupture status reported by the sponsor. Shading of these represents implants included in determination of silent rupture rate.

Figure 3 (continued): Flowchart of Rupture – Core Revision Cohort



Notes: 1. Information in brackets indicates method of initial suspicion of rupture reported by the sponsor.
2. Information in parentheses indicates final rupture status reported by the sponsor. Shading of these represents implants included in determination of silent rupture rate.

Complications following implant replacement:
Of the 24 patients (41 implants) who underwent implant removal with replacement through 3 years, **complications following replacement** (in this case it is the second replacement) were reported in 9 patients (10 implants): swelling (3 patients), redness (3 patients), breast pain (2 patients), bruising (2 patients), capsular contracture (1 patient), infection (1 patient), implant malposition (1 patient), hypertrophic/abnormal scarring (2 patients), and seroma/fluid accumulation (2 patients). Note that these values are not additive because an implant/patient may have reported more than one occurrence of a complication. Risk rates are not shown due to the small sample.

D. General Complications—Core Revision Cohort

Before breast implantation, 44 of the 225 patients (19.6%) reported the following 46 **reproductive problems**: infertility (9 reports), spontaneous abortion (32 reports), planned abortion (1 report), and ectopic pregnancy (4 reports). Through 3 years after breast implantation, there were 6 patients (2.7%) reporting 7 reproductive problems: 3 reports of infertility (2 of these patients reported infertility pre-implant as well), 3 reports of spontaneous abortion, and 1 report of hysterectomy for unknown reason. Without information on the number of patients attempting reproduction (which was not collected in the Core Study) and without a comparison group of age-matched patients with similar co-morbidities, and followed for the same duration, it is not possible to draw definitive conclusions from these data; however, the percentage of patients reporting a problem post-implantation is lower than that pre-implantation. This could be due to less reproductive attempts or to reporting bias.

Before breast implantation, of the 122 patients who attempted to breast feed, 24 patients (19.7%) reported the following 27 **lactation problems**: pain (8 reports), inadequate milk production (7 reports), mastitis requiring treatment (6 reports), mastitis not requiring treatment (2 reports), excess milk production (2 reports), "baby wouldn't nurse" (1 report), and duct disruption from previous surgery (1 report). Through 3 years after breast implantation, of the 9 patients who attempted to breast feed, 4 patients (44.4%) reported the following 5 lactation problems: 1 report of mastitis requiring treatment and 4 reports of inadequate milk production. Following implantation, of the 4 patients reporting a problem with lactation, all reported inadequate milk production. Although the proportion of women with lactation problems following breast implantation is higher than before implantation, the numbers following implantation are small and may not be reliable. Of those women attempting to breast feed and reporting a problem with lactation, a higher proportion reported inadequate milk production following implantation; however, the numbers are small and may, therefore, be unreliable.

Prior to breast implantation, there were 67 of 225 patients (29.8%) who reported **breast disease**, with 42 of these patients having confirmed malignant breast disease and 25 having benign disease. Through 3 years, there were 16 patient reports of post-implant breast disease, all of which were benign. Note that 3 of these patients also had a pre-implant report of benign breast disease in the same breast.

Prior to breast implantation, 125 of 225 patients had a pre-implant **mammogram**. The readings were normal or benign in 120 of these, and confirmed malignant in 5 patients. Through 3 years following breast implantation, 94 patients had a mammogram, of which 7 were reported

abnormal. Of these 7 patients abnormal mammograms, 3 patients were determined to have no breast disease (one of these patients had a similar pre-implant report in the same breast) and 4 were determined to have benign breast disease.

With respect to **connective tissue/autoimmune disease (CTD)**, there was one patient with confirmed rheumatoid arthritis prior to revision. Through 2 years, there was one new report of a CTD: a 50 year old patient developed fibromyalgia 11 months after implant revision. The sponsor was asked to provide physician notes and laboratory results to document this diagnosis. Review of this information indicates that the patient's chief complaint was fatigue, myalgias, difficulty falling asleep, and difficulty staying asleep for several years (onset was not documented) with worsening over the few months preceding her referral to a rheumatologist. Her other significant medical problems include a history of irregular heart beat for which she takes inderal and history of goiter/chronic thyroiditis prior to her initial breast implantation (which was for augmentation) for which she takes synthroid. Her review of symptoms was significant for denial of gastrointestinal and genitourinary symptoms. On physical examination, tender points were noted in the shoulders and trapezii bilaterally without evidence of synovitis of upper or lower extremities, with tenderness over the trochanteric and anserine bursae. Laboratory results are significant for negative RF and ANA, ESR of 7, with a normal CBC, LFT's, CK, and aldolase. The patient was given rofecoxib and a muscle relaxant. The reported prevalence of fibromyalgia is 3.4% in women, and the estimated annual incidence is reported to be 1% per year in the general U.S. population. Without a control group of women without implants but with similar age, demographics, and risk factors with which to compare, associations with breast implantation cannot be made regarding this one patient.

Recall that the sponsor collected **CTD signs and symptoms** from the patients at baseline and at follow-up in the Activities and Lifestyle questionnaire to assist in determining CTD diagnoses, if present. This self-administered questionnaire includes a Modified Health Assessment Questionnaire (MHAQ), which assesses ability to perform various physical functions of daily living, and it includes a variety of signs and symptoms related to rheumatic diseases and to general health. Of the 225 Core Revision patients, data are available for 157 patients (69.8%). These data are summarized in **Table 33** below. Recall that the intention of this questionnaire is to identify patients who warrant additional evaluation and referral to a rheumatologist. Without a control/comparison group of patients without implants followed for the same duration of follow-up and with similar demographic characteristics, conclusions cannot be made from these data.

Table 33: Summary of signs/symptom categories reported through 2 years after implantation—Core Revision.

Sign/Symptom Category	Pre-implant N = 386	Through 2 years post-implant N = 386
Skin[1]	13 (8.3%)	24 (15.3%)
Muscle[2]	46 (29.3%)	62 (39.5%)
Joint[3]	41 (26.1%)	56 (35.7%)
Neurological[4]	59 (37.6%)	78 (49.7%)
General[5]	55 (35.0%)	66 (42.0%)
Other[6]	28 (17.8%)	34 (21.7%)
Gastointestinal[7]	44 (28.0%)	56 (35.7%)
Urinary[8]	5 (3.2%)	13 (8.3%)

Notes: [1]Includes hair loss, skin rash, facial swelling, ecchymosis, purpura, unusual bruising, unusual bleeding, hives, other skin problem.
[2]Includes muscle weakness, muscle pain/aches/cramps, back pain, neck pain.
[3]Includes joint pain, swelling of hands, swelling of other joints, morning stiffness.
[4]Includes memory problems, problems with thinking, headaches, numbness/tingling of arms/legs, losing balance, ringing in ears.
[5]Includes fever, swollen glands, weight loss, weight gain, fatigue, generalized pain.
[6]Includes dry eyes, other eye problems, sores in mouth, dry mouth, problems with taste, trouble swallowing.
[7]Includes heartburn, stomach pain/cramps, nausea, vomiting, constipation, diarrhea, dark stool, blood in stool, loss of appetite, and moderate or greater gastrointestinal trouble.
[8]Includes urinating too often, problems with urination.

E. Additional Analyses of Safety Data—Core Revision Cohort

The sponsor performed Cox proportional hazards regression analysis to determine whether the complications of reoperation, implant replacement/removal, implant rupture, capsular contracture, and infection were associated with patient age (≤40 years vs. >40 years), antibiotic pocket irrigation (yes vs. no), betadine pocket irrigation (yes vs. no), implant placement (submuscular vs. other), incision site (periareolar vs. inframammary vs. axillary vs. other), device texture (smooth vs. textured), and device shape (round vs. contoured), as suggested in FDA's Guidance document on Breast Implants. This information was based on an earlier date of database closure of August 30, 2002. There were no significant findings with respect to these analyses.

F. Effectiveness—Core Revision Cohort

The sponsor did not collect **breast size** information for the revision patients.

The sponsor collected both patient and physician **satisfaction**. Because the patient satisfaction is more relevant, I will omit summarizing the physician satisfaction information. The sponsor collected both general patient satisfaction and satisfaction based on pre-operative expectation of satisfaction. With respect to **general patient satisfaction**, of the 173 patient (of 225) who completed this questionnaire at years, there was a small decline in mean satisfaction from the 0-4 week timepoint of 4.4 (SD 0.8) to 4.4 (SD 1.1) at 2 years. With respect to **patient satisfaction compared to pre-operative expectation** of satisfaction, of the 129 of 225 patients (58.4%) who responded to these patient satisfaction questions, the majority of patients reported being satisfied or very satisfied with their implants at both 1 and 2 years post-implant. At 2 years, approximately 10.1% of these patients reported being dissatisfied or very dissatisfied, with 9.3% reporting being neutral regarding their satisfaction compared to their pre-operative expectations. There were small but statistically significant declines in mean patient satisfaction at both 1 and 2 years compared to pre-operative expectations of satisfaction. The mean pre-operative expectation of satisfaction value of 4.7 (SD 0.5) was compared to 4.2 (SD 1.1) at 2 years.

With respect to **Health Status Questionnaire (SF-36 and MOS-20)**, the core revision cohort reported statistically significantly higher levels at baseline compared to normative population data for all subscales of the SF-36. At 2 years, all subscales declined for the revision cohort, but were still either higher or comparable to normative population values. **Table 34** summarizes the results of selected health status measures. Note that most of the changes, even those that are worse, are small.

Table 34: Summary of selected health status/QOL measures—Core Revision Cohort.

Assessment Method	Statistically significant change in pre- to 2 year post-implant score	Direction of Change
SF-36 Role Emotional	Yes	Worse
SF-36 Role Physical	No	Worse
SF-36 General Health	Yes	Worse
SF-36 Pain	No	Worse
SF-36 Social	Yes	Worse
SF-36 Physical	No	Worse
Vitality	No	Worse
Mental Health	Yes	Worse
MOS-20 Health Perceptions	Yes	Worse
MOS-20 Physical Functioning	No	Worse
MOS-20 Role Functioning	No	Worse
MOS-20 Social Functioning	No	Worse
MOS-20 Mental Health	Yes	Worse
TSCS Physical Self	Yes	Worse
Rosenberg Self Esteem	Yes	Worse
Semantic Differential	No	No Change
Body Esteem-Total Score	No	Worse
Body Esteem-Sexual Attractiveness	No	Better
Body Esteem-Weight Concern	No	Worse
Body Esteem-Physical Condition	Yes	Worse

VI. ADJUNCT STUDY RESULTS—RECONSTRUCTION

A. Patient Disposition—Adjunct Reconstruction Cohort

Enrollment of the reconstruction patients in the Adjunct Study occurred between December of 1997 and August of 2002, with a date of database closure of August 30, 2002. Recall that there is no enrollment limit set for this study, as it was intended to provide access to breast implants (silicone gel-filled implants were the only breast implants available at the time) while collecting short-term local complications; therefore, enrollment and follow-up is ongoing. The follow-up period for this study is 5 years after implantation.

There were **15,465 reconstruction patients (26,935 implants)** enrolled for the purpose of unilateral or bilateral breast reconstruction by 1,272 principle investigators at 2,355 sites.

Because follow-up visits are at 1, 3, and 5 years and the first patient enrolled in the amended protocol was in May of 1998, the maximum duration of follow-up from regularly scheduled visits is 3 years. Of the 15,465 patients, 10,453 patients (67.6%) had reached their 1 year follow-up visit and 2,567 patients (16.6%) had reached their 3 year follow-up visit (including a 6 month window) at the time of database closure. Patient disposition at 1 and 3 years is summarized in **Table 35** below. The majority of deaths reported are those of recurrent or metastatic breast

cancer and appear to be unrelated to the implants. The follow-up rate in this study is less than optimal.

Table 35: Cumulative Patient disposition at 1 and 3 years on a by-patient basis—Adjunct Reconstruction Cohort.

	1 Year	3 Years
Number of Patients (Devices) Enrolled	15,465 patients 26,935 devices	15,465 patients 26,935 devices
Theoretical Follow-up[1]	10,453 patients	2, 567 patients
Expected Follow-up[2]	10,291	2,482
Actual Follow-up (%)[3]	5,537 (53.8%)	670 (27.0%)
Total Withdrawals[4]	4,916	1,897
Deaths[5]	28	16
Implant Removal without Replacement[5,6]	134	69
Lost to follow-up[7]	4,754	1,812

Notes: [1]Based on follow-up to 14 months for the 1 year visit and 38 months for the 3 year visit due to an additional 2 month window.
[2]Expected follow-up is theoretical minus deaths and implant removals without replacement.
[3]Percent follow-up is actual divided by expected follow-up.
[4]Includes deaths, implant removals without replacement, and lost to follow-up.
[5]Based on follow-up to 18 months for the 1 year visit and 42 months for the 3 year visit.
[6]Defined as removal without replacement of all study implants.
[7]Includes patients who discontinued by choice.

B. Demographic/Baseline Characteristics—Adjunct Reconstruction Cohort

All product styles were used in this cohort. The three most common styles used in descending order are style 153 (textured, contoured, 31.7%), style 110 (round, textured, 23.9%), and style 40 (round, smooth, 20.2%). Textured implants were used in approximately two-thirds of the cases. Styles 10 and 20 were used in a minimal of cases. Intraoperative complications were reported in 95 of the patients.

With respect to demographic characteristics, the median age is 44 years (range 14 to 98 years) and is less than the 50 years (range 26 to 82) of the Core Reconstruction Cohort. This may be because the Core Study has a minimal age of 18 years listed as an inclusion criteria, while the Adjunct Study has no minimal age limit specified in the inclusion criteria.

C. Local Complications—Adjunct Reconstruction

Table 36 summarizes the 3 year cumulative Kaplan-Meier (KM) risk rates of first occurrence occurring in ≥ 1% of patients, reported on a by-patient basis.

Table 36: By patient cumulative Kaplan-Meier (KM) risk rates of first occurrence (95% confidence interval) of local complications[1] occurring in ≥ 1%[2] at 3 years of follow-up—Adjunct Reconstruction Cohort.

	Adjunct Reconstruction N = 15,465 Patients	
Complication	Rate	(95% CI)
Asymmetry[1]	16.3%	(14.4%, 18.2%)
Breast Pain[1]	7.9%	(6.5%, 9.3%)
Bruising	2.9%	(2.1%, 3.6%)
Capsular Contracture III/IV	17.6%	(15.7%, 19.4%)
Capsule Calcification[1]	3.2%	(2.3%, 4.2%)
Hematoma	1.5%	(0.8%, 2.1%)
Hypertrophic Scarring	6.9%	(5.7%, 8.1%)
Implant Extrusion	1.3%	(0.6%, 2.0%)
Implant Malposition[1]	8.5%	(7.1%, 9.9%)
Implant Rupture[3]	1.6%	(0.9%, 2.4%)
Infection	2.6%	(1.7%, 3.4%)
Irritation[1]	1.0%	(0.5%, 1.5%)
Lymphadenopathy	1.5%	(0.8%, 2.2%)
Nipple Complications[1,4]	7.1%	(5.8%, 8.4%)
Other	3.4%	(2.3%, 4.4%)
Palpability/Visibility[1]	11.8%	(10.2%, 13.4%)
Pneumothorax	1.0%	(0.4%, 1.7%)
Redness	3.8%	(2.9%, 4.7%)
Removal/Replacement	28.2%	(26.1%, 30.3%)
Reoperation	44.1%	(42.0%, 46.2%)
Seroma	1.8%	(1.1%, 2.5%)
Skin Sensation Changes[1,5]	3.0%	(2.2%, 3.7%)
Skin Rash	1.7%	(1.0%, 2.4%)
Swelling	6.3%	(5.2%, 7.3%)
Tissue/Skin Necrosis	1.3%	(0.7%, 1.9%)
Wrinkling/Rippling[1]	9.4%	(7.9%, 10.8%)

Notes: [1]Includes reports of only ≥ moderate severity for the complications of asymmetry, breast pain, capsule calcification, delayed wound healing, implant malposition, irritation/inflammation, loss of nipple sensation, nipple complications, palpability/visibility, skin sensation changes, and wrinkling.
[2]Delayed wound healing (0.8%) not shown.
[3]There were 45 implants reported as ruptured in 36 patients through 3 years.
[4]Refers to nipple paresthesia, hypersensitivity, or loss of nipple sensation.
[5]Refers to skin paresthesia or hypersensitivity.

With respect to **reoperation**, there were 2,034 patients (2,577 implants) through 3 years experiencing at least one reoperation. Most patients underwent one reoperation (88.5% of reoperations). There were a total of 2,341 reoperations performed in this cohort of patients. Although the sponsor collected the indication and type of reoperation procedure, they did not

provide this information. Given that the percent follow-up is so low for this cohort, these data may not be reliable and, therefore, will not be requested.

There were 63 patients (74 implants) experiencing at least one complication following implant replacement. The major types of complications in this respect were asymmetry, followed by capsular contracture, malposition, and wrinkling.

D. Effectiveness—Adjunct Reconstruction Cohort

The sponsor collected both patient and physician satisfaction. Because the patient satisfaction is more relevant, I will omit the physician satisfaction information. The number of patients completing satisfaction case report forms was not provided by the sponsor. Of the patients responding to patient satisfaction questions, at both 1 and 3 years, approximately 80% of the patients reported being satisfied or definitely satisfied. Approximately 7% of patients at 1 and 3 years reported being definitely or somewhat dissatisfied.

VII. ADJUNCT STUDY—REVISION

A. Patient Disposition—Adjunct Revision Cohort

Enrollment of the revision patients in the Adjunct Study occurred between April of 1998 and August of 2002, with a date of database closure of August 30, 2002. Recall that there is no enrollment limit set for this study, as it was intended to provide access to breast implants (silicone gel-filled implants were the only breast implants available at the time) while collecting short-term local complications; therefore, enrollment and follow-up is ongoing. The follow-up period for this study is 5 years after implantation.

There were 9,902 patients implanted/enrolled for the purpose of revision of an existing implant (and in some cases with contralateral augmentation) by 1,272 principle investigators and 2,355 sites. Because 21 patients were subsequently found to be ineligible because of inclusion/exclusion criteria violations, the sponsor is reporting on **9,881 patients (19,099 implants)**.

Of the 9,881 patients, 74.1% had reached their 1 year and 23.9% had reached their 3 year visit (including a 6 month window) at the time of database closure. Patient disposition at 1 and 3 years is summarized in **Table 37** below. There were 14 deaths reported through 3 years (+ 6 months) due the following: 5 due to cancer (2 breast, 1 lung, 1 brain, and 1 unknown primary), 3 due to suicide, 2 due to murder, 1 due to advanced age, 1 due to heart failure, 1 due to renal failure, and 1 due to stroke. The follow-up rate in this study is less than optimal, and less than that of the Adjunct Reconstruction Study.

Table 37: Cumulative patient disposition at 1 and 3 years on a by-patient basis—Adjunct Revision Cohort.

	1 Year	3 Years
Number of Patients (Devices)	9,881 patients 19,099 devices	9,881 patients 19,099 devices
Theoretical Follow-up[1]	7,322	2,365
Expected Follow-up[2]	7,244	2,310
Actual Follow-up (%)[3]	3,180 (43.9%)	460 (19.9%)
Total Withdrawals[4]	4,142	1,905
Deaths[5]	10	5
Implant Removal without Replacement[5,6]	68	50
Lost to follow-up[7]	4,064	1,850

Notes: [1]Based on follow-up to 14 months for the 1 year visit and 38 months for the 3 year visit due to an additional 2 month window.
[2]Expected follow-up is theoretical minus deaths and implant removals without replacement.
[3]Percent follow-up is actual divided by expected follow-up.
[4]Includes deaths, implant removals without replacement, and lost to follow-up.
[5]Based on follow-up to 18 months for the 1 year visit and 42 months for the 3 year visit.
[6]Defined as removal without replacement of all study implants.
[7]Includes patients who discontinued by choice.

B. Demographic/Baseline Characteristics—Adjunct Revision Cohort

With respect to demographic characteristics, the median age of 44 years (range 18 to 88 years) is similar to that of the Core Revision Cohort. All product styles were used in this cohort. The three most common styles used in descending order are style 40 (round, smooth, 31.3%), style 110 (round, textured, 29.9%), and style 45 (round, smooth, 14.3%). Styles 10 and 12 were used in a minimal of cases. Intraoperative complications were reported in 54 patients.

C. Local Complications—Adjunct Revision Cohort

Table 38 summarizes the cumulative 3 year KM risk rates of first occurrence of local complications.

Table 38: By patient cumulative Kaplan-Meier (KM) risk rates of first occurrence (95% confidence interval) of local complications[1] occurring in ≥ 1%[2] at 3 years of follow-up—Adjunct Revision Cohort.

	Adjunct Revision N = 9,881 Patients	
Complication	Rate	(95% CI)
Asymmetry[1]	9.8%	(7.9%, 11.6%)
Breast Pain[1]	7.8%	(6.1%, 9.4%)
Bruising	3.2%	(2.6%, 3.8%)
Capsular Contracture III/IV	20.0%	(17.6%, 22.3%)
Capsule Calcification[1]	3.4%	(2.3%, 4.5%)
Hypertrophic Scarring	4.4%	(3.4%, 5.4%)
Implant Malposition[1]	7.3%	(5.6%, 8.9%)
Implant Rupture[3]	2.7%	(1.4%, 3.9%)
Infection	1.4%	(0.9%, 2.0%)
Lymphadenopathy	1.5%	(0.8%, 2.2%)
Nipple Complications[1,4]	5.5%	(4.1%, 6.9%)
Other	2.3%	(1.6%, 3.1%)
Palpability/Visibility[1]	13.6%	(11.4% 15.8%)
Redness	2.6%	(1.7%, 3.4%)
Removal/Replacement	24.1%	(21.7%, 26.5%)
Reoperation	34.5%	(31.9%, 37.0%)
Seroma	1.5%	(0.7%, 2.2%)
Skin Sensation Changes[1,5]	2.0%	(1.2%, 2.8%)
Skin Rash	1.9%	(1.0%, 2.8%)
Swelling	6.1%	(5.0%, 7.2%)
Wrinkling/Rippling[1]	10.6%	(8.7%, 12.5%)

Notes: [1]Includes reports of only ≥ moderate severity for the complications of asymmetry, breast pain, capsule calcification, delayed wound healing, implant malposition, irritation/inflammation, loss of nipple sensation, nipple complications, palpability/visibility, skin sensation changes, and wrinkling.
[2]Delayed wound healing (0.6%), hematoma (0.9%), implant extrusion (0.6%), irritation (0.4%), pneumothorax (0.5%), tissue/skin necrosis (0.9%), not shown.
[3]There were 45 implants reported as ruptured in 36 patients through 3 years.
[4]Refers to nipple paresthesia, hypersensitivity, or loss of nipple sensation.
[5]Refers to skin paresthesia or hypersensitivity.

With respect to **reoperation**, there were 892 patients (1,248 implants) experiencing at least one reoperation procedure through 3 years. Most patients underwent one reoperation (91.4%). There were a total of 982 reoperations performed in this cohort of patients. Although the sponsor collected the indication and type of reoperation procedure, they did not provide this information. Given that the percent follow-up is so low for this cohort, these data may not be reliable and, therefore, will not be requested.

There were 28 patients (36 implants) experiencing at least one complication following implant replacement. The major types of complications in this respect were visibility, followed by palpability, wrinkling, and capsular contracture.

D. Effectiveness—Adjunct Revision Cohort

The sponsor collected both patient and physician satisfaction. Because the patient satisfaction is more relevant, I will omit the physician satisfaction information. The number of patients completing satisfaction case report forms was not provided by the sponsor. Of the patients responding to patient satisfaction questions, at both 1 and 3 years, approximately 80% of patients reported being satisfied or definitely satisfied at both 1 and 3 years. Approximately 10% of patients reported being definitely or somewhat dissatisfied at both 1 and 3 years.

VIII. 1990 STUDY SUMMARY

The McGhan 1990 Mammary Implant Study (AR 90 Study) was a prospective, open label study which collected local complications safety information. This study utilized 11 styles of implants, only 4 of which the sponsor is currently seeking approval in this PMA: style 40 (73 augmentation implants), style 110 (230 augmentation and 3 reconstruction implants), style 120 (78 augmentation and 2 reconstruction implants), and style 153 (27 reconstruction implants). There were 547 augmentation patients (1,093 implants), and 29 reconstruction patients (43 implants) included in the sponsor's report for all implant styles. Of the implant styles for which the sponsor is seeking approval, there are 381 augmentation implants in 192 patients and 32 reconstruction implants in 23 patients. The median age for the entire cohort is 31 years for the augmentation patients, and 43 years for the reconstruction patients.

Of note, approximately 28% of augmentation implants and 10% of reconstruction implants had antibiotic and/or steroid and/or betadine injected into the implant, a practice which is currently not performed due to reports of rupture/leakage/necrosis/extrusion associated with these practices. Follow-up rates at 5 years were approximately 70% for augmentation patients and 78% for reconstruction patients. There were 3 augmentation deaths (1 due to suicide and 2 to lung cancer), and no reconstruction patient deaths. Because of the small number of reconstruction patients, the focus of this summary will be on the augmentation group. **Table 39** below summarizes selected KM risk rates at 5 years for the augmentation patients in the AR 90 Study, including only those implant styles for which the sponsor is seeking approval.

Table 39: By patient cumulative KM risk rates of first occurrence (95% CI) of selected complications in augmentation patients for styles 40, 110, 120, and 153).

Complication	A90 Study 5 Years N = 192 Patients	
	Rate	(95% CI)
Reoperation	26.3%	(19.5%, 33.1%)
Breast Pain	25.8%	(18.8%, 32.7%)
Palpability/ Visibility	23.3%	(16.7%, 30.0%)
Wrinkling	12.8%	(7.6%, 18.0%)
Asymmetry	15.3%	(9.5%, 21.1%)
Loss of Nipple Sensation	17.2%	(11.5%, 22.9%)
Nipple Paresthesia	20.2%	(14.1%, 26.3%)
Skin Paresthesia	15.2%	(9.7%, 20.6%)
Capsular Contracture	14.9%	(9.2%, 20.7%)
Removal/ Replacement	11.5%	(6.4%, 16.5%)
Rupture	4.0%	(0.5%, 7.6%)
Infection	1.1%	(0.0%, 2.5%)

IX. HEALTH EFFECTS IN THE LITERATURE

Because the Core and Adjunct Studies are designed to collect primarily local complications, the sponsor provided a summary of the historical published literature to address the potential long term and general health effects of the implants, focusing on a summary of the literature from 1991-2002. In preparation for this PMA submission, FDA conducted its own search of the published literature from 1998 to 2002 to assess the significant publications published since the IOM report (Institute of Medicine National Academy Press, 2000). The following topics were searched in relation to breast implants: silent rupture, gel migration, imaging, neurological diseases, cancer, pediatric/offspring effects, connective tissue disease including fibromyalgia, lactation, and pregnancy/reproduction. The following is a brief summary of the IOM report findings and a summary of significant references published following the IOM report to 2002 based on this literature search.

A. Lactation

There is concern both about the quality and quantity of breast milk following breast implantation. Since the IOM report, there have been no substantially new studies to address this issue. The few studies published to address quality, measured silicon in breast milk and found similar or lower levels in breast implant recipients than that in non-implanted women, cow's milk, or infant formula. The few studies regarding quantity in women with either silicone or saline breast implants are retrospective and indicate that lactation insufficiency is reported in 28 to 64% of women, particularly with the periareolar approach. These rates are comparable to that reported in the Core Study.

B. Pregnancy/Reproduction/Pediatric/Offspring Effects

Concern regarding an association of esophageal disease in children mothered by women with implants and immune effects in children of mothers with implants has been expressed. The IOM

report concluded that evidence for an association of maternal silicone breast implants and children's health effects is insufficient or flawed, and that no biologically plausible causation has been suggested. The IOM report additionally concluded that evidence of toxic effects of silicone during or after pregnancy is lacking. Since that report, three publications have been published which address this issue: **Kjoller et al., 2002; Signorello, et al. 2001; Fryzek, et al., 2000, and Brinton, et al., 2000**. Taken together, these publications do not indicate a greater risk of reproductive risk, congenital malformation, or immune effects in children of women with implants compared to women undergoing breast reduction surgery or other cosmetic surgery procedures.

C. Cancer

With respect to **breast cancer**, the IOM concluded that there are sufficient studies with consistent and convincing findings of no association between breast cancer and implants in a cosmetic population. IOM further concluded that the data indicate that implants do not increase breast cancer recurrence rates or decrease survival rates in patients after reconstruction with implants. Following the IOM report, **Brinton, LA, et al., 2000** reported on a retrospective cohort of 13,488 patients who underwent cosmetic breast implant surgery, reviewing questionnaires and death certificates to assess long term health effects, and comparing findings to general population rates and to an internal comparison group of 3,936 patients undergoing other, non-breast implant cosmetic surgery at the same physician practices. Although breast tumors tended to be detected at a somewhat later stage among breast implant recipients compared to the internal comparison group, the difference was not statistically significant, nor was there any significant difference in breast cancer mortality between the two groups. The authors concluded that breast implants do not appear to alter the risk of subsequent breast cancer in a cosmetic population.

With respect to **other cancers**, the IOM concluded that there is insufficient evidence for an association between silicone breast implants and multiple myeloma, monoclonal gammopathy of undetermined significance (MGUS), solid tumors, or lymphoma. Following the IOM report, **Brinton, LA, et al., 2001** reported on the same cohort described above. While, like previous investigations, higher risks of cervical, vulvar, and lung cancers among women with cosmetic implants compared to the general population were found, when compared to the internal control population of non-implant cosmetic surgery, only the risk of lung cancer (RR = 2.23) was statistically higher, and the risk of brain cancer (specifically glioblastoma multiforme) was elevated (RR = 2.83) but not statistically higher. The authors state that because these elevated risks were defined on the basis of death certificates, interpretation requires caution. With respect to MGUS, **Karlson, EW, et al., 2001** conducted a retrospective study of the Nurses' Health Study to assess the risk of MGUS compared to age-matched non-implant exposed women. The authors found no substantial increase in MGUS in women exposed to breast implants.

In another related reference by **Brinton, LA, et al., 2001** regarding mortality among the same cohort of patients, indicated a higher overall mortality among implant patients compared to the internal control patients (RR = 1.27), which was reflected by increases in respiratory tract cancers (SMR = 3.03), brain cancer (SMR = 2.25), and suicide (SMR = 4.24).

Mellemkjaer, L, et al., 2000 reported on 1,653 women who underwent cosmetic breast implant surgery and 1,736 women attending the same clinics for other reasons during 1973-1995,

updating their previous report of 1,114 women, and following the women for cancer through the Danish Cancer Registry. Standardized incidence ratios of breast and other cancers was not significantly different between these groups.

While these studies address common cancers, rare cancers cannot be adequately assessed in these studies. For example, **Gaudet's, G., et al., 2002** case report of 2 patients with anaplastic large cell T-cell lymphoma of the breast--an unusual type of breast lymphoma considering that breast lymphoma is a rare entity in itself and consists mostly of B-cell lymphomas in older women—cannot be confirmed with the above epidemiologic studies. Note that the sponsor collected information on breast cancer in the Core Study. This study was not designed to collect information on other cancers.

D. Connective Tissue Disease including Fibromyalgia

Since the Institute of Medicine's conclusions of insufficient evidence to support an association of silicone breast implants with CTD or with atypical CTD, there have been no studies in the published literature to date which suggest an association of breast implants with a specific CTD. In searching the medical literature from 1998 to 2002, there have been a few significant epidemiological studies published which relate to this issue and which are summarized below.

Kjoller, et al., 2001 published a retrospective case-control study conducted from 1977 to 1994 of the prevalence of CTD conditions in women with cosmetic implants and without implants in 8 of 27 plastic surgery clinics in Denmark, comparing them to that reported for hospitalized patients in the Danish National Registry of Patients. The authors found no excess of definite CTD in the implant cohort. For unspecified rheumatism, statistically significant excesses were observed for both the implant and control cohorts when compared with national rates.

Englert, et al., 2001 reported a population-based retrospective case-control study to determine the incidence and/or prevalence of autoimmune and CTD in female residents of Sydney, Australia in women with augmentation mammoplasty compared with females with non-silicone associated plastic surgery between 1979 and 1983. There was no difference in the occurrence of CTD or CTD-related parameters (such as carpal tunnel syndrome, digital vasospasm, sicca symptoms, tendonitis, livedo reticularis, abnormal nailfold capillaroscopy), thyroid disorders, fibromyalgia, or multiple sclerosis between cohorts. Axillary adenopathy and low titer positive antinuclear antibody (ANA) occurred with significantly greater frequency in the cases. Higher titers of ANA, which is clinically more significant than low titer ANA, were not significantly different between the groups. Note that this reference was not provided and not included in the sponsor's PMA; however, an earlier publication by the author was included.

Fryzek, et al., 2001 published a retrospective cohort study of 28 self-reported symptoms (ranging from painful joints to constipation) in women with cosmetic breast implants and with cosmetic breast reduction surgery between 1965 and 1993 taken from the Swedish Inpatient Registry. Questionnaire completion rates were 65% and 72% for these respective cohorts. Symptoms were more frequently reported by the women with implants compared to those with breast reduction. This study was funded by Dow-Corning Corporation.

On the issue of a **new or undifferentiated CTD** associated with breast implants, **Laing, et al., 2001** published a retrospective case-control study of women diagnosed with undifferentiated

connective tissue disease (UCTD) between 1980 and 1992 and exposures to silicone-containing and non-silicone-containing medical devices in Michigan and Ohio. 205 UCTD cases and 2,095 controls selected by random digit dialing were selected. When all silicone containing devices (including shunts and catheters) are considered, a significant association was observed (odds ratio, OR, 2.81); however, the OR for exposure to breast implants was increased but not significantly (OR 2.22), even when multiple adjustments were made. This study was funded, in part, by Dow-Corning Corporation.

On the issue of **fibromyalgia (FM)** and breast implants, **Wolfe, et al. 1999** reported a case-control study of patients seen at the Arthritis Research Center at the University of Kansas School of Medicine between 1991 and 1994. 464 patients with RA, 508 with FM, and 261 with osteoarthritis (OA) were compared to 503 randomly selected controls. The authors previously reported in an abstract in1995 the lack of association of breast implants and RA, OA, and FM. The current study formally presented the data in the 1995 study. No association between pre-disease silicone filled breast implantation and FM was detected regardless of the control group used (OR 1.22). No association was found with RA as well (OR 1.66) compared to the combined control groups. The lead author for this report has been retained as an expert witness by Dow Chemical.

On the issue of FM, **Lai, et al., 2000** examined the medical records in a single rheumatology practice in Atlanta of 2500 women seen between 1986 and 1992 in this uncontrolled retrospective cohort study. Univariate and multivariate regression analyses indicated significant associations between FM and hypermobility (OR 2.2), and between hypermobility and breast implantation (OR 1.8), but no association was found between breast implantation and subsequent FM (OR 0.74). **Brown, et al., 2002** evaluated self-reported FM diagnosis in women with and without ruptured silicone breast implants in this uncontrolled retrospective cohort study. Women with extra-capsular gel noted on MRI examination were twice as likely to report a diagnosis of FM (OR 2.7) compared to women without extracapsular gel noted on MRI.

A reference published by **Janowsky, et al., 2000** and not cited by Inamed Corporation in their PMA, summarized the previously published data on CTD and breast implants in a meta-analysis. No associations were found between breast implants in general, or silicone gel-filled breast implants specifically, and individual CTD's, all definite CTD's combined, or other rheumatic or autoimmune conditions.

With respect to **autoantibody development** following breast implantation, **Karlson, et al., 1999** studied women from the prospective cohort of the Nurse's Health Study. The authors randomly selected 200 women who had been exposed to silicone breast implants and who never reported a CTD during 14 years of follow-up and 500 age-matched, nonexposed women, including some women with definite CTD, some with at least one symptom of a CTD, and healthy controls. There were no statistically significantly higher levels of autoantibodies in women with implants compared to healthy controls with the exception of anti-ssDNA antibodies, which has an unknown clinical relevance. Another study by **Karlson, et al., 2001** evaluated women selected from the run-in phase of the Women's Health Study for autoantibodies and serologic factors suggesting immune activation. The authors found isolated decreased complement levels C3 and C4 in women with breast implants compared to women without breast implants and to women

with diabetes, without corresponding elevations in antinuclear antibody levels or of elevated monoclonal immunoglobulin levels, suggesting a spurious finding.

In summary, the published literature following the IOM report does not support an association of breast implants and CTD. This literature cannot completely address rare diseases, such as CTDs. There are references which suggest that there may be a subset of women with breast implants who may be more susceptible to having FM; however, the characteristics which define this subset has not been defined, and these findings have not been confirmed.

E. Neurological Disease

The IOM concluded that the available studies suggesting an association with neurological disease—with the exception of local nerve compression due to implant rupture and migration—have deficits which limit conclusions to be drawn from them, and that the evidence for a neurological disease or syndrome caused by or associated with silicone breast implants is insufficient or flawed. Since the IOM report, **Winther, JF, et al., 2001** published additional follow-up of the Danish cohort of 1,653 women with cosmetic breast implant surgery at private clinics in Denmark compared to a comparison cohort of 1,736 women who underwent other types of cosmetic procedures. No increased risks for neurological disorders were found in the breast implant recipients. Note that these studies are limited in that rare disorders cannot be addressed.

F. Rupture/Gel Migration

With respect to gel-filled breast implants and rupture, the IOM report contains primarily retrospective explant or MRI cohorts, which were reported through 1999. Estimates of rupture for gel implants cited in the IOM report ranged from 0.3-77%. The IOM estimated that approximately less than 10% of modern gel implants would have ruptured by five years and that ruptures would continue to accumulate and prevalence would increase over time. They also stated that silicone gel fluid permeation of the shell seems to have a deleterious effect on implant durability.

Since the IOM report, **Brown SL, et al., 2000** published a study of an unreferred population of women with implants of varying ages from varying manufacturers who underwent MRI screening for detection of rupture. The median age of implants in this study was 16.5 years (range of 6.4 to 28.0 years) and the majority of women had implants for augmentation. The authors found 68.6% of the women (55% of implants) had at least one ruptured implant when a consensus of radiologists' determination is used to define rupture. Of those ruptured implants in which the manufacturer was known, 10% were McGhan implants.

In a similar study, **Holmich, LR, et al., 2001** reports on a cohort of 271 women with 533 cosmetic breast implants who were randomly selected from 4 plastic surgery clinics in Denmark to undergo MRI screening for rupture. The authors found that overall, 26% of implants in 36% of the women examined were found to be ruptured, and an additional 6% of implants were possibly ruptured. Of the ruptured implants, 22% were extracapsular, and these were significantly associated with a history of closed capsulotomy.

With respect to silicone gel migration, there are reports of silicone migration to the axilla, arm, or abdominal wall. There are a few cases reported in the literature of granulomas surrounding

birefringent material in axillary lymph nodes and the upper extremities, as well as local inflammatory reactions to free silicone in ruptured implants. An investigation by **Gaubitz, M, et al., 2002** discusses the finding of silicone in the liver as estimated by magnetic resonance spectroscopy in a selected cohort of women with MRI-intact implants, presumably due to gel bleed.

G. Breast Implant Imaging

The IOM report noted MRI to be the most accurate imaging modality for detection of intra- and extracapsular rupture. The literature after the IOM report on this subject has not indicated new findings. Note that interference with mammography is a known risk of breast implants, necessitating additional compressive views and additional radiation for performing mammography. The sponsor's prospective studies were not designed to collect data on interference with mammography.

X. SUMMARY/CONCLUSIONS

With respect to **local complications, Tables 40, 41, and 42** summarize selected local complication rates reported in all of the sponsor's prospective studies of gel-filled breast implants. Although it is not appropriate to compare these rates to those reported for the sponsor's saline-filled breast implants, the rates are similar. With respect to the Core Study, the sponsor's precision for estimating the risk rate are consistent with that proposed in the sample size estimation.

With respect to **asymptomatic rupture**, screening for this event has been performed in only a subset of the patients, in only the Core Study, and for only the first of 5 planned serial screenings. And yet, the majority of implant ruptures in the Core Study were detected from MRI screening, and do not include microscopically determined ruptures. For the Core Study, of the 15 implant ruptures confirmed by explant, 9 implant ruptures **(60%) were asymptomatic** and were detected by MRI screening at approximately one year after implantation in a subset of 597 of the 1780 implants (33.5%) enrolled in the study. If all ruptures included in the sponsor's rupture rate are considered--including those classified as "unconfirmed"-- then of the 26 total implant ruptures, 15 implant ruptures were asymptomatic and detected only from MRI screening. If the proportion of patients screened for asymptomatic rupture was larger, the reported rupture rate would be higher as well.

Given these limitations in the ascertainment of asymptomatic rupture, there is concern regarding the determination of both asymptomatic ruptures and the total rupture rate. Questions to the Panel pertaining to safety and to labeling attempt to describe these concerns. Note that because for the Adjunct Study and the 1990 Study, MRI screening for rupture was not performed, rupture rate comparisons between these studies and the Core Study may not be appropriate.

With respect to potential **general health effects** (i.e. not local complications) and potential **long term health effects**, the sponsor has utilized the published literature and animal data—which have inherent limitations of specificity and applicability--to address these issues. There is concern whether these data adequately characterize the potential general (i.e. non-local) health effects and potential long term health effects of the implants. A question to the Panel attempts to describe these concerns.

With respect to **efficacy**, while the majority of those patients responding to satisfaction questionnaires report satisfaction with their implants, quality of life indices actually worsened over time for the Augmentation and Revision patients, although these changes were small and were still higher when compared to normative data. When patient satisfaction is assessed as compared to expectation of satisfaction, mean satisfaction values worsened over time for all cohorts in the Core Study. Although the sponsor has collected effectiveness data, the benefit of implants for a patient is likely an individual one, which is difficult to quantify and may not be appropriately grouped into a summed or mean value. This needs to be taken into consideration given that the risks and benefits for an individual indication may differ, and that breast implantation is an elective procedure.

Table 40: By-patient cumulative Kaplan-Meier (KM) risk rates of first occurrence (95% confidence interval) of selected local complications through 3 years—Core Augmentation and 1990 Study.

	Core Augmentation N = 494 Patients		1990 Augmentation N = 192 Patients	
Complication	Rate	(95% CI)	Rate	(95% CI)
Capsular Contracture III/IV	8.3%	(5.8%, 10.9%)	9.5%	(5.0%, 13.9%)
Reoperation	20.6%	(16.8%, 24.4%)	19.9%	(13.9%, 25.8%)
Removal/replacement	7.5%	(5.0%, 10.0%)	6.3%	(2.7%, 9.8%)
Implant Rupture	1.2%	(0.1%, 2.2%)	0.6%	(0.0%, 1.7%)
Infection	1.0%	(0.1%, 1.9%)	1.1%	(0.0%, 2.5%)

Table 41: By-patient cumulative Kaplan-Meier (KM) risk rates of first occurrence (95% confidence interval) of selected local complications through 3 years—Core Reconstruction and Adjunct Reconstruction.

	Core Reconstruction N = 221 Patients		Adjunct Reconstruction N = 15,465 Patients	
Complication	Rate	(95% CI)	Rate	(95% CI)
Capsular Contracture III/IV	16.1%	(8.7%, 23.6%)	17.6%	(15.7%, 19.4%)
Reoperation	45.9%	(36.8%, 55.1%)	44.1%	(42.0%, 30.3%)
Removal/replacement	25.3%	(16.9%, 33.6%)	28.2%	(26.1%, 30.3%)
Implant Rupture	6.3%	(1.3%, 11.3%)	1.6%	(0.9%, 2.4%)
Infection	2.3%	(0.0%, 5.4%)	2.6%	(1.7%, 3.4%)

Table 42: By-patient cumulative Kaplan-Meier (KM) risk rates of first occurrence (95% confidence interval) of selected local complications through 3 years—Core Revision and Adjunct Revision.

	Core Revision N = 225 Patients		Adjunct Revision N = 9,881 Patients	
Complication	Rate	(95% CI)	Rate	(95% CI)
Capsular Contracture III/IV	9.8%	(5.7%, 13.9%)	20.0%	(17.6%, 22.3%)
Reoperation	33.4%	(26.9%, 39.8%)	34.5%	(31.9%, 37.0%)
Removal/replacement	13.4%	(8.7%, 18.1%)	24.1%	(21.7%, 26.5%)
Implant Rupture	3.6%	(1.0%, 6.3%)	2.7%	(1.4%, 3.9%)
Infection	2.8%	(0.6%, 4.9%)	1.4%	(0.9%, 2.0%)

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